# BORTEZOMIB

**Hetero Labs Ltd.**

Chemwatch Hazard Alert Code: **2**

Chemwatch: **4157-10**
Version No: **3.1.1.1**
Safety Data Sheet

Issue Date: **18/08/2014**
Print Date: **07/04/2016**
Initial Date: **Not Available**
L.GHS.IND.EN

## SECTION 1 IDENTIFICATION OF THE SUBSTANCE / MIXTURE AND OF THE COMPANY / UNDERTAKING

### Product Identifier

| | |
|---|---|
| **Product name** | BORTEZOMIB |
| **Chemical Name** | bortezomib |
| **Synonyms** | C19-H25-B-N4-O4, PS-341, Pyz-Phe-borLeu, Velcade, [(1R)-3-methyl-1-({(2S-3-phenyl-2-[(pyrazin-2-ylcarbonyl)amino]propanoyl}amino)-, antineoplastic/ cytotoxic, butyl] boronic acid, protease inhibitor, pyrazinoic acid, phenylalanine, leucine, boric acid, tripeptide proteasome inhibitor |
| **Chemical formula** | C19H25BN4O4 |
| **Other means of identification** | Not Available |
| **CAS number** | 179324-69-7 |

### Relevant identified uses of the substance or mixture and uses advised against

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|---|---|
| **Relevant identified uses** | For treating relapsed multiple myeloma and mantle cell lymphoma. In multiple myeloma, complete clinical responses have been obtained in patients with otherwise refractory or rapidly advancing disease. Given by intravenous injection. The first therapeutic proteasome inhibitor tested in humans. Proteasomes are enzymes found in cells, and play a role in regulating cell function and growth. The boron atom in bortezomib binds the catalytic site of the 26S proteasome[2] with high affinity and specificity. In normal cells, the proteasome regulates protein expression and function by degradation of ubiquitinylated proteins, and also cleanses the cell of abnormal or misfolded proteins. Clinical and preclinical data support a role in maintaining the immortal phenotype of myeloma cells, and cell-culture and xenograft data support a similar function in solid tumor cancers. While multiple mechanisms are likely to be involved, proteasome inhibition may prevent degradation of pro-apoptotic factors, permitting activation of programmed cell death in neoplastic cells dependent upon suppression of pro-apoptotic pathways. |

### Details of the supplier of the safety data sheet

| | |
|---|---|
| **Registered company name** | Hetero Labs Ltd. |
| **Address** | Hetero Corporate, 7-2-A2, Industrial Estate, Sanath Nagar, Hyderabad Telengana 500018 India |
| **Telephone** | +91 40 23704923 |
| **Fax** | Not Available |
| **Website** | www.heterodrugs.com |
| **Email** | Not Available |

### Emergency telephone number

| | |
|---|---|
| **Association / Organisation** | Not Available |
| **Emergency telephone numbers** | Not Available |
| **Other emergency telephone numbers** | Not Available |

## SECTION 2 HAZARDS IDENTIFICATION

### Classification of the substance or mixture

#### CHEMWATCH HAZARD RATINGS

| | Min | Max |
|---|---|---|
| Flammability | 1 | |
| Toxicity | 1 | |
| Body Contact | 0 | |
| Reactivity | 1 | |
| Chronic | 2 | |

0 = Minimum
1 = Low
2 = Moderate
3 = High
4 = Extreme

**NFPA 704 diamond**


Note: The hazard category numbers found in GHS classification in section 2 of this SDSs are NOT to be used to fill in the NFPA 704 diamond. Blue = Health Red = Fire Yellow = Reactivity White = Special (Oxidizer or water reactive substances)

#### CANADIAN WHMIS SYMBOLS

Continued...

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| **Classification** | Reproductive Toxicity Category 2 |

### Label elements

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| **GHS label elements** |  |
| SIGNAL WORD | **WARNING** |

### Hazard statement(s)

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| **H361** | Suspected of damaging fertility or the unborn child. |

### Precautionary statement(s) Prevention

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| **P201** | Obtain special instructions before use. |
| **P280** | Wear protective gloves/protective clothing/eye protection/face protection. |

### Precautionary statement(s) Response

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

### Precautionary statement(s) Storage

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| **P405** | Store locked up. |

### Precautionary statement(s) Disposal

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| **P501** | Dispose of contents/container in accordance with local regulations. |

## SECTION 3 COMPOSITION / INFORMATION ON INGREDIENTS

### Substances

| CAS No | %[weight] | Name | Classification |
|---|---|---|---|
| 179324-69-7 | >98 | bortezomib | Reproductive Toxicity Category 2; H361 |

### Mixtures

See section above for composition of Substances

## SECTION 4 FIRST AID MEASURES

### Description of first aid measures

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| **Eye Contact** | If this product comes in contact with the eyes:<br>▸ Wash out immediately with fresh running water.<br>▸ Ensure complete irrigation of the eye by keeping eyelids apart and away from eye and moving the eyelids by occasionally lifting the upper and lower lids.<br>▸ Seek medical attention without delay; if pain persists or recurs seek medical attention.<br>▸ Removal of contact lenses after an eye injury should only be undertaken by skilled personnel. |
| **Skin Contact** | If skin or hair contact occurs:<br>▸ Flush skin and hair with running water (and soap if available).<br>▸ Seek medical attention in event of irritation. |
| **Inhalation** | ▸ If fumes, aerosols or combustion products are inhaled remove from contaminated area.<br>▸ Other measures are usually unnecessary. |
| **Ingestion** | ▸ If swallowed do **NOT** induce vomiting.<br>▸ If vomiting occurs, lean patient forward or place on left side (head-down position, if possible) to maintain open airway and prevent aspiration.<br>▸ Observe the patient carefully.<br>▸ Never give liquid to a person showing signs of being sleepy or with reduced awareness; i.e. becoming unconscious.<br>▸ Give water to rinse out mouth, then provide liquid slowly and as much as casualty can comfortably drink.<br>▸ Seek medical advice. |

### Indication of any immediate medical attention and special treatment needed

For employees potentially exposed to antineoplastic and/ or cytotoxic agents on a regular basis, a preplacement physical examination and history (noting risk factors) is recommended. Periodic follow-up examinations should also be undertaken and should be overseen by a physician familiar with the toxic effects of the substance and full details of the nature of work undertaken by the employee.
Following administration of antineoplastics, control of nausea and vomiting may be attempted by giving phenothiazines such as perphenazine, prochlorperazine, promethazine or thiethylperazine. In bone-marrow depression, transfusion of blood or platelets reduces the risk of life-threatening haemorrhage. Granulocyte transfusions and injection of antibiotics may be necessary to combat infection in the neutropenic patient. Hyperuricaemia is avoided by the addition of allopurinol to treatment schedules and measures such as alkalisation of the urine and hydration may be adopted.
MARTINDALE: The Extra Pharmacopoeia, 28th Edition.

## SECTION 5 FIREFIGHTING MEASURES

**Continued...**

### Extinguishing media

- Foam.
- Dry chemical powder.
- BCF (where regulations permit).
- Carbon dioxide.
- Water spray or fog - Large fires only.

### Special hazards arising from the substrate or mixture

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| **Fire Incompatibility** | ‣ Avoid contamination with oxidising agents i.e. nitrates, oxidising acids, chlorine bleaches, pool chlorine etc. as ignition may result |

### Advice for firefighters

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| **Fire Fighting** | ‣ Alert Fire Brigade and tell them location and nature of hazard.<br>‣ Wear breathing apparatus plus protective gloves.<br>‣ Prevent, by any means available, spillage from entering drains or water courses.<br>‣ Use water delivered as a fine spray to control fire and cool adjacent area.<br>‣ **DO NOT** approach containers suspected to be hot.<br>‣ Cool fire exposed containers with water spray from a protected location.<br>‣ If safe to do so, remove containers from path of fire.<br>‣ Equipment should be thoroughly decontaminated after use. |
| **Fire/Explosion Hazard** | ‣ Combustible solid which burns but propagates flame with difficulty; it is estimated that most organic dusts are combustible (circa 70%) - according to the circumstances under which the combustion process occurs, such materials may cause fires and / or dust explosions.<br>‣ Organic powders when finely divided over a range of concentrations regardless of particulate size or shape and suspended in air or some other oxidizing medium may form explosive dust-air mixtures and result in a fire or dust explosion (including secondary explosions).<br>‣ Avoid generating dust, particularly clouds of dust in a confined or unventilated space as dusts may form an explosive mixture with air, and any source of ignition, i.e. flame or spark, will cause fire or explosion. Dust clouds generated by the fine grinding of the solid are a particular hazard; accumulations of fine dust (420 micron or less) may burn rapidly and fiercely if ignited - particles exceeding this limit will generally not form flammable dust clouds; once initiated, however, larger particles up to 1400 microns diameter will contribute to the propagation of an explosion.<br>‣ In the same way as gases and vapours, dusts in the form of a cloud are only ignitable over a range of concentrations; in principle, the concepts of lower explosive limit (LEL) and upper explosive limit (UEL) are applicable to dust clouds but only the LEL is of practical use; - this is because of the inherent difficulty of achieving homogeneous dust clouds at high temperatures (for dusts the LEL is often called the "Minimum Explosible Concentration", MEC).<br>‣ When processed with flammable liquids/vapors/mists,ignitable (hybrid) mixtures may be formed with combustible dusts. Ignitable mixtures will increase the rate of explosion pressure rise and the Minimum Ignition Energy (the minimum amount of energy required to ignite dust clouds - MIE) will be lower than the pure dust in air mixture. The Lower Explosive Limit (LEL) of the vapour/dust mixture will be lower than the individual LELs for the vapors/mists or dusts.<br>‣ A dust explosion may release of large quantities of gaseous products; this in turn creates a subsequent pressure rise of explosive force capable of damaging plant and buildings and injuring people.<br>‣ Usually the initial or primary explosion takes place in a confined space such as plant or machinery, and can be of sufficient force to damage or rupture the plant. If the shock wave from the primary explosion enters the surrounding area, it will disturb any settled dust layers, forming a second dust cloud, and often initiate a much larger secondary explosion. All large scale explosions have resulted from chain reactions of this type.<br>‣ Dry dust can be charged electrostatically by turbulence, pneumatic transport, pouring, in exhaust ducts and during transport.<br>‣ Build-up of electrostatic charge may be prevented by bonding and grounding.<br>‣ Powder handling equipment such as dust collectors, dryers and mills may require additional protection measures such as explosion venting.<br>‣ All movable parts coming in contact with this material should have a speed of less than 1-meter/sec.<br>‣ A sudden release of statically charged materials from storage or process equipment, particularly at elevated temperatures and/ or pressure, may result in ignition especially in the absence of an apparent ignition source.<br>‣ One important effect of the particulate nature of powders is that the surface area and surface structure (and often moisture content) can vary widely from sample to sample, depending of how the powder was manufactured and handled; this means that it is virtually impossible to use flammability data published in the literature for dusts (in contrast to that published for gases and vapours).<br>‣ Autoignition temperatures are often quoted for dust clouds (minimum ignition temperature (MIT)) and dust layers (layer ignition temperature (LIT)); LIT generally falls as the thickness of the layer increases.<br>Combustion products include; carbon monoxide (CO) carbon dioxide ($CO_2$) nitrogen oxides (NOx) metal oxides, other pyrolysis products typical of burning organic materialMay emit poisonous fumes. |

## SECTION 6 ACCIDENTAL RELEASE MEASURES

### Personal precautions, protective equipment and emergency procedures

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| **Minor Spills** | It is recommended that areas handling final finished product have cytotoxic spill kits available.<br>Spill kits should include:<br>‣ impermeable body covering,<br>‣ shoe covers,<br>‣ latex and utility latex gloves,<br>‣ goggles,<br>‣ approved respirator (AS/NZS 1716 & 1715, EN 143:2000 & 149:2001, ANSI Z88 or national equivalent), see Section 8,<br>‣ disposable dust pan and scoop,<br>‣ absorbent towels,<br>‣ spill control pillows,<br>‣ disposable sponges,<br>‣ sharps container,<br>‣ disposable garbage bag and<br>‣ hazardous waste label<br><br>Where spills are treated with loose absorbents, such as vermiculite, ensure dust exposure is strictly avoided.<br>To avoid accidental exposure due to waste handling of cytotoxics:<br>‣ Place waste residue in a segregated sealed plastic container.<br>‣ Used syringes, needles and sharps should not be crushed, clipped, recapped, but placed directly into an approved sharps container.<br>‣ Dispose of any cleanup materials and waste residue according to all applicable laws and regulations e.g, secure chemical landfill disposal.<br>‣ Clean up waste regularly and abnormal spills immediately.<br>‣ Avoid breathing dust and contact with skin and eyes.<br>‣ Wear protective clothing, gloves, safety glasses and dust respirator.<br>‣ Use dry clean up procedures and avoid generating dust.<br>‣ Vacuum up or sweep up. **NOTE:** Vacuum cleaner must be fitted with an exhaust micro filter (HEPA type) (consider explosion-proof machines designed to be grounded during storage and use).<br>‣ Dampen with water to prevent dusting before sweeping.<br>‣ Place in suitable containers for disposal. |

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| | All personnel likely to involved in a antineoplastic (cytotoxic) spill must receive practical training in:<br>▸ the correct procedures for handling cytotoxic drugs or waste in order to prevent and minimise the risk of spills<br>▸ the location of the spill kit in the area<br>▸ the arrangements for medical treatment of any affected personnel<br>▸ the procedure for containment of the spill, and decontamination of personnel and the environment, including the different procedures for major and minor spills<br>▸ the procedure for waste disposal according to the nature and extent of the spill |
| **Major Spills** | Moderate hazard.<br>▸ **CAUTION**: Advise personnel in area.<br>▸ Alert Emergency Services and tell them location and nature of hazard.<br>▸ Control personal contact by wearing protective clothing.<br>▸ Prevent, by any means available, spillage from entering drains or water courses.<br>▸ Recover product wherever possible.<br>▸ **IF DRY:** Use dry clean up procedures and avoid generating dust. Collect residues and place in sealed plastic bags or other containers for disposal. **IF WET:** Vacuum/shovel up and place in labelled containers for disposal.<br>▸ **ALWAYS:** Wash area down with large amounts of water and prevent runoff into drains.<br>▸ If contamination of drains or waterways occurs, advise Emergency Services. |

Personal Protective Equipment advice is contained in Section 8 of the SDS.

## SECTION 7 HANDLING AND STORAGE

### Precautions for safe handling

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| **Safe handling** | Australian Standard (AS2639) and the National Institute of Health (USA) recommends that the preparation of injectable antineoplastic drugs should be performed in a Class II laminar flow biological safety cabinet and that personnel preparing drugs of this class should wear appropriate personal protective gear. Emphasise controls on containment.<br>▸ Avoid all personal contact, including inhalation.<br>▸ Wear protective clothing when risk of exposure occurs.<br>▸ Use in a well-ventilated area.<br>▸ Prevent concentration in hollows and sumps.<br>▸ **DO NOT** enter confined spaces until atmosphere has been checked.<br>▸ **DO NOT** allow material to contact humans, exposed food or food utensils.<br>▸ Avoid contact with incompatible materials.<br>▸ When handling, **DO NOT** eat, drink or smoke.<br>▸ Keep containers securely sealed when not in use.<br>▸ Avoid physical damage to containers.<br>▸ Always wash hands with soap and water after handling.<br>▸ Work clothes should be laundered separately. Launder contaminated clothing before re-use.<br>▸ Use good occupational work practice.<br>▸ Observe manufacturer's storage and handling recommendations contained within this SDS.<br>▸ Atmosphere should be regularly checked against established exposure standards to ensure safe working conditions are maintained.<br>▸ Organic powders when finely divided over a range of concentrations regardless of particulate size or shape and suspended in air or some other oxidizing medium may form explosive dust-air mixtures and result in a fire or dust explosion (including secondary explosions)<br>▸ Minimise airborne dust and eliminate all ignition sources. Keep away from heat, hot surfaces, sparks, and flame.<br>▸ Establish good housekeeping practices.<br>▸ Remove dust accumulations on a regular basis by vacuuming or gentle sweeping to avoid creating dust clouds.<br>▸ Use continuous suction at points of dust generation to capture and minimise the accumulation of dusts. Particular attention should be given to overhead and hidden horizontal surfaces to minimise the probability of a "secondary" explosion. According to NFPA Standard 654, dust layers 1/32 in.(0.8 mm) thick can be sufficient to warrant immediate cleaning of the area.<br>▸ Do not use air hoses for cleaning.<br>▸ Minimise dry sweeping to avoid generation of dust clouds. Vacuum dust-accumulating surfaces and remove to a chemical disposal area. Vacuums with explosion-proof motors should be used.<br>▸ Control sources of static electricity. Dusts or their packages may accumulate static charges, and static discharge can be a source of ignition.<br>▸ Solids handling systems must be designed in accordance with applicable standards (e.g. NFPA including 654 and 77) and other national guidance.<br>▸ Do not empty directly into flammable solvents or in the presence of flammable vapors.<br>▸ The operator, the packaging container and all equipment must be grounded with electrical bonding and grounding systems. Plastic bags and plastics cannot be grounded, and antistatic bags do not completely protect against development of static charges.<br>Empty containers may contain residual dust which has the potential to accumulate following settling. Such dusts may explode in the presence of an appropriate ignition source.<br>▸ Do NOT cut, drill, grind or weld such containers.<br>▸ In addition ensure such activity is not performed near full, partially empty or empty containers without appropriate workplace safety authorisation or permit. |
| **Other information** | Antineoplastics (cytotoxics):<br>▸ should be clearly identifiable to all personnel involved in their handling<br>▸ should be stored in impervious break-resistant containers<br>▸ should be stored in separate, clearly marked storage areas to minimise the risk of breakage, and to limit contamination in the event of leakage.<br>Spill kits should be available in storage areas.<br>▸ Store in original containers.<br>▸ Keep containers securely sealed.<br>▸ Store in a cool, dry area protected from environmental extremes.<br>▸ Store away from incompatible materials and foodstuff containers.<br>▸ Protect containers against physical damage and check regularly for leaks.<br>▸ Observe manufacturer's storage and handling recommendations contained within this SDS.<br>For major quantities:<br>▸ Consider storage in bunded areas - ensure storage areas are isolated from sources of community water (including stormwater, ground water, lakes and streams}.<br>▸ Ensure that accidental discharge to air or water is the subject of a contingency disaster management plan; this may require consultation with local authorities. |

### Conditions for safe storage, including any incompatibilities

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| **Suitable container** | ▸ Glass container is suitable for laboratory quantities<br>▸ Polyethylene or polypropylene container.<br>▸ Check all containers are clearly labelled and free from leaks. |

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| **Storage incompatibility** | ▸ Avoid reaction with oxidising agents |

## SECTION 8 EXPOSURE CONTROLS / PERSONAL PROTECTION

### Control parameters

**OCCUPATIONAL EXPOSURE LIMITS (OEL)**

**INGREDIENT DATA**

Not Available

**EMERGENCY LIMITS**

| Ingredient | Material name | TEEL-1 | TEEL-2 | TEEL-3 |
|---|---|---|---|---|
| BORTEZOMIB | Not Available | Not Available | Not Available | Not Available |

| Ingredient | Original IDLH | Revised IDLH |
|---|---|---|
| bortezomib | Not Available | Not Available |

**MATERIAL DATA**

It is the goal of the ACGIH (and other Agencies) to recommend TLVs (or their equivalent) for all substances for which there is evidence of health effects at airborne concentrations encountered in the workplace.
At this time no TLV has been established, even though this material may produce adverse health effects (as evidenced in animal experiments or clinical experience). Airborne concentrations must be maintained as low as is practically possible and occupational exposure must be kept to a minimum.
**NOTE:** The ACGIH occupational exposure standard for Particles Not Otherwise Specified (P.N.O.S) does NOT apply.
CEL TWA: 0.001 mg/m3
(CEL=Chemwatch Exposure Limit)

### Exposure controls

**Appropriate engineering controls**

**For potent pharmacological agents:**
**Powders**
To prevent contamination and overexposure, no open handling of powder should be allowed.
- Powder handling operations are to be done in a powders weighing hood, a glove box, or other equivalent ventilated containment system.
- In situations where these ventilated containment hoods have not been installed, a non-ventilated enclosed containment hood should be used.
- Pending changes resulting from additional air monitoring data, up to 300 mg can be handled outside of an enclosure provided that no grinding, crushing or other dust-generating process occurs.
- An air-purifying respirator should be worn by all personnel in the immediate area in cases where non-ventilated containment is used, where significant amounts of material (e.g., more than 2 grams) are used, or where the material may become airborne (as through grinding, etc.).
- Powder should be put into solution or a closed or covered container after handling.
- If using a ventilated enclosure that has not been validated, wear a half-mask respirator equipped with HEPA cartridges until the enclosure is validated for use.

**Solutions Handling:**
- Solutions can be handled outside a containment system or without local exhaust ventilation during procedures with no potential for aerosolisation. If the procedures have a potential for aerosolisation, an air-purifying respirator is to be worn by all personnel in the immediate area.
- Solutions used for procedures where aerosolisation may occur (e.g., vortexing, pumping) are to be handled within a containment system or with local exhaust ventilation.
- In situations where this is not feasible (may include animal dosing), an air-purifying respirator is to be worn by all personnel in the immediate area. If using a ventilated enclosure that has not been validated, wear a half-mask respirator equipped with HEPA cartridges until the enclosure is validated for use.
- Ensure gloves are protective against solvents in use.

**Unless written procedures, specific to the workplace are available, the following is intended as a guide:**
- **For Laboratory-scale handling of Substances assessed to be toxic by inhalation. *Quantities of up to 25 grams*** may be handled in Class II biological safety cabinets *; ***Quantities of 25 grams to 1 kilogram*** may be handled in Class II biological safety cabinets* or equivalent containment systems; ***Quantities exceeding 1 kg*** may be handled either using specific containment, a hood or Class II biological safety cabinet*,
- HEPA terminated local exhaust ventilation should be considered at point of generation of dust, fumes or vapours.
- The need for respiratory protection should also be assessed where incidental or accidental exposure is anticipated. Dependent on levels of contamination, PAPR, full face air purifying devices with P2 or P3 filters or air supplied respirators should be evaluated. When handling: ***Quantities of up to 25 grams***, an approved respirator with HEPA filters or cartridges should be considered; ***Quantities of 25 grams to 1 kilogram,*** a half-face negative pressure, full negative pressure, or powered helmet-type air purifying respirator should be considered. ***Quantities in excess of 1 kilogram*****,** a full face negative pressure, helmet-type air purifying, or supplied air respirator should be considered.

Written procedures, specific to a particular work-place, may replace these recommendations
* For Class II Biological Safety Cabinets, Types B2 or B3 should be considered. Where only Class I, open fronted Cabinets are available, glove panels may be added, Laminar flow cabinets do not provide sufficient protection when handling these materials unless especially designed to do so.
**Pilot Plant and Production**
- Wear appropriate gloves; lab coat, nylon coveralls or disposable Tyvek suit; safety glasses, safety shoes, and disposable booties. Use good manufacturing practices (i.e., cGMPs).
- Protective garment (coveralls, Tyvek, lab coat) is not to be worn outside the work area.
- Clean/dirty/decontamination areas are to be established.
- Negative/positive air pressure relationships and buffer zones required (i.e., ante-room/degowning room/airlock).
- Area access is to be restricted.
- High-energy operations such as milling, particle sizing, spraying or fluidising should be done within an approved emission control or containment system.
- Develop cleaning procedures and techniques that limit potential exposure

**Personal protection**

**Eye and face protection**

- Chemical protective goggles with full seal.
- Shielded mask (gas-type).
- Contact lenses may pose a special hazard; soft contact lenses may absorb and concentrate irritants. A written policy document, describing the wearing of lenses or restrictions on use, should be created for each workplace or task. This should include a review of lens absorption and adsorption for the class of chemicals in use and an account of injury experience. Medical and first-aid personnel should be trained in their removal and suitable equipment should be readily available. In the event of chemical exposure, begin eye irrigation immediately and remove contact lens as soon as practicable. Lens should be removed at the first signs of eye redness or irritation - lens should be removed in a clean environment only after workers have washed hands thoroughly. [CDC NIOSH Current Intelligence Bulletin 59], [AS/NZS 1336 or national equivalent]

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| **Skin protection** | See Hand protection below |
| **Hands/feet protection** | The selection of suitable gloves does not only depend on the material, but also on further marks of quality which vary from manufacturer to manufacturer. Where the chemical is a preparation of several substances, the resistance of the glove material can not be calculated in advance and has therefore to be checked prior to the application.<br>The exact break through time for substances has to be obtained from the manufacturer of the protective gloves and.has to be observed when making a final choice.<br>Suitability and durability of glove type is dependent on usage. Important factors in the selection of gloves include:<br>▸ frequency and duration of contact,<br>▸ chemical resistance of glove material,<br>▸ glove thickness and<br>▸ dexterity<br>Select gloves tested to a relevant standard (e.g. Europe EN 374, US F739, AS/NZS 2161.1 or national equivalent).<br>▸ When prolonged or frequently repeated contact may occur, a glove with a protection class of 5 or higher (breakthrough time greater than 240 minutes according to EN 374, AS/NZS 2161.10.1 or national equivalent) is recommended.<br>▸ When only brief contact is expected, a glove with a protection class of 3 or higher (breakthrough time greater than 60 minutes according to EN 374, AS/NZS 2161.10.1 or national equivalent) is recommended.<br>▸ Some glove polymer types are less affected by movement and this should be taken into account when considering gloves for long-term use.<br>▸ Contaminated gloves should be replaced.<br>Gloves must only be worn on clean hands. After using gloves, hands should be washed and dried thoroughly. Application of a non-perfumed moisturiser is recommended.<br>▸ Rubber gloves (nitrile or low-protein, powder-free latex, latex/ nitrile). Employees allergic to latex gloves should use nitrile gloves in preference.<br>▸ Double gloving should be considered.<br>▸ PVC gloves.<br>▸ Change gloves frequently and when contaminated, punctured or torn.<br>▸ Wash hands immediately after removing gloves.<br>▸ Protective shoe covers. [AS/NZS 2210]<br>▸ Head covering.<br>Experience indicates that the following polymers are suitable as glove materials for protection against undissolved, dry solids, where abrasive particles are not present.<br>▸ polychloroprene.<br>▸ nitrile rubber.<br>▸ butyl rubber.<br>▸ fluorocaoutchouc.<br>▸ polyvinyl chloride.<br>Gloves should be examined for wear and/ or degradation constantly. |
| **Body protection** | See Other protection below |
| **Other protection** | ▸ When handling antineoplastic materials, it is recommended that a disposable work-uniform (such as Tyvek or closed front surgical-type gown with knit cuffs) is worn.<br>▸ Potentially contaminated bodily fluids should be handled in accordance with local standards or codes of practice (appendix 10 of 'Cytotoxic Drugs and Related Waste' - Workcover New South Wales, HSE Information Sheet MISC615, OSHA Technical Manual (OTM) Section VI: Chapter 2)<br>▸ For quantities up to 500 grams a laboratory coat may be suitable.<br>▸ For quantities up to 1 kilogram a disposable laboratory coat or coverall of low permeability is recommended. Coveralls should be buttoned at collar and cuffs.<br>▸ For quantities over 1 kilogram and manufacturing operations, wear disposable coverall of low permeability and disposable shoe covers.<br>▸ For manufacturing operations, air-supplied full body suits may be required for the provision of advanced respiratory protection.<br>▸ Eye wash unit.<br>▸ Ensure there is ready access to an emergency shower.<br>▸ For Emergencies: Vinyl suit |
| **Thermal hazards** | Not Available |

### Respiratory protection

Particulate. (AS/NZS 1716 & 1715, EN 143:000 & 149:001, ANSI Z88 or national equivalent)

| Required Minimum Protection Factor | Half-Face Respirator | Full-Face Respirator | Powered Air Respirator |
|---|---|---|---|
| up to 10 x ES | P1<br>Air-line* | -<br>- | PAPR-P1<br>- |
| up to 50 x ES | Air-line** | P2 | PAPR-P2 |
| up to 100 x ES | - | P3 | - |
| | | Air-line* | - |
| 100+ x ES | - | Air-line** | PAPR-P3 |

* - Negative pressure demand ** - Continuous flow
A(All classes) = Organic vapours, B AUS or B1 = Acid gasses, B2 = Acid gas or hydrogen cyanide(HCN), B3 = Acid gas or hydrogen cyanide(HCN), E = Sulfur dioxide(SO2), G = Agricultural chemicals, K = Ammonia(NH3), Hg = Mercury, NO = Oxides of nitrogen, MB = Methyl bromide, AX = Low boiling point organic compounds(below 65 degC)

## SECTION 9 PHYSICAL AND CHEMICAL PROPERTIES

### Information on basic physical and chemical properties

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| **Appearance** | Solid; does not mix well with water. The solubility of bortezomib, as the monomeric boronic acid, is 3.3 to 3.8 mg/mL in a pH range of 2 to 6.5. |

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| **Physical state** | Divided Solid | **Relative density (Water = 1)** | Not Available |
| **Odour** | Not Available | **Partition coefficient n-octanol / water** | Not Available |
| **Odour threshold** | Not Available | **Auto-ignition temperature (°C)** | Not Available |
| **pH (as supplied)** | Not Applicable | **Decomposition temperature** | Not Available |

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|---|---|---|---|
| **Melting point / freezing point (°C)** | Not Available | **Viscosity (cSt)** | Not Applicable |
| **Initial boiling point and boiling range (°C)** | Not Applicable | **Molecular weight (g/mol)** | 384.24 |
| **Flash point (°C)** | Not Available | **Taste** | Not Available |
| **Evaporation rate** | Not Applicable | **Explosive properties** | Not Available |
| **Flammability** | Not Available | **Oxidising properties** | Not Available |
| **Upper Explosive Limit (%)** | Not Available | **Surface Tension (dyn/cm or mN/m)** | Not Applicable |
| **Lower Explosive Limit (%)** | Not Available | **Volatile Component (%vol)** | Negligible |
| **Vapour pressure (kPa)** | Negligible | **Gas group** | Not Available |
| **Solubility in water (g/L)** | Partly miscible | **pH as a solution (1%)** | Not Applicable |
| **Vapour density (Air = 1)** | Not Applicable | **VOC g/L** | Not Available |

## SECTION 10 STABILITY AND REACTIVITY

| | |
|---|---|
| **Reactivity** | See section 7 |
| **Chemical stability** | ▸ Unstable in the presence of incompatible materials.<br>▸ Product is considered stable.<br>▸ Hazardous polymerisation will not occur. |
| **Possibility of hazardous reactions** | See section 7 |
| **Conditions to avoid** | See section 7 |
| **Incompatible materials** | See section 7 |
| **Hazardous decomposition products** | See section 5 |

## SECTION 11 TOXICOLOGICAL INFORMATION

### Information on toxicological effects

| | |
|---|---|
| **Inhaled** | The material is not thought to produce either adverse health effects or irritation of the respiratory tract following inhalation (as classified by EC Directives using animal models). Nevertheless, adverse systemic effects have been produced following exposure of animals by at least one other route and good hygiene practice requires that exposure be kept to a minimum and that suitable control measures be used in an occupational setting.<br>Persons with impaired respiratory function, airway diseases and conditions such as emphysema or chronic bronchitis, may incur further disability if excessive concentrations of particulate are inhaled.<br>If prior damage to the circulatory or nervous systems has occurred or if kidney damage has been sustained, proper screenings should be conducted on individuals who may be exposed to further risk if handling and use of the material result<br>in excessive exposures. |
| **Ingestion** | Accidental ingestion of the material may be damaging to the health of the individual.<br>Antineoplastic action is dependent on cytotoxic action which is not selective for malignant cells alone but may affect all rapidly dividing cells. The spectrum of effects seen with these agents is therefore similar although differences do arise. Acute adverse effects commonly produced by these agents include anorexia, nausea and vomiting (often central in origin and occurring minutes or hours after administration), allergic reaction (skin rashes, pruritus, erythema, hypotension, malaise, and anaphylaxis) and local irritant effects. Hyperuricaemia and acute renal failure (due to uric acid nephropathy) may result from the lysis of large numbers of cells and breakdown of nucleoproteins. |
| **Skin Contact** | The material is not thought to produce adverse health effects or skin irritation following contact (as classified by EC Directives using animal models). Nevertheless, good hygiene practice requires that exposure be kept to a minimum and that suitable gloves be used in an occupational setting.<br>Open cuts, abraded or irritated skin should not be exposed to this material<br>Entry into the blood-stream through, for example, cuts, abrasions, puncture wounds or lesions, may produce systemic injury with harmful effects. Examine the skin prior to the use of the material and ensure that any external damage is suitably protected. |
| **Eye** | Although the material is not thought to be an irritant (as classified by EC Directives), direct contact with the eye may cause transient discomfort characterised by tearing or conjunctival redness (as with windburn). Slight abrasive damage may also result. The material may produce foreign body irritation in certain individuals. |
| **Chronic** | Exposure to the material may cause concerns for human fertility, generally on the basis that results in animal studies provide sufficient evidence to cause a strong suspicion of impaired fertility in the absence of toxic effects, or evidence of impaired fertility occurring at around the same dose levels as other toxic effects, but which are not a secondary non-specific consequence of other toxic effects.<br><br>Exposure to the material may cause concerns for humans owing to possible developmental toxic effects, generally on the basis that results in appropriate animal studies provide strong suspicion of developmental toxicity in the absence of signs of marked maternal toxicity, or at around the same dose levels as other toxic effects but which are not a secondary non-specific consequence of other toxic effects.<br>On the basis, primarily, of animal experiments, concern has been expressed by at least one classification body that the material may produce carcinogenic or mutagenic effects; in respect of the available information, however, there presently exists inadequate data for making a satisfactory assessment.<br><br>Long term exposure to high dust concentrations may cause changes in lung function (i.e. pneumoconiosis) caused by particles less than 0.5 micron penetrating and remaining in the lung. A prime symptom is breathlessness. Lung shadows show on X-ray.<br>Delayed or long-term effects may result from the action of antineoplastic agents on rapidly dividing normal cells in the bone marrow, lymphoreticular tissue, gastrointestinal mucosa, skin, gonads and foetus. The most common of these is bone-marrow depression with leucopenia, anaemia, thrombocytopenia and bleeding. Immunosuppressant effects involve both antibody and cell-mediated immunity and may increase susceptibility to infection and increase the risk of haemorrhage, both potentially life-threatening. GI effects may include stomatitis, mouth ulcers, oesophagitis, abdominal pain, haemorrhage, diarrhoea and intestinal ulceration and perforation. Reversible baldness (alopecia) may result from the action of theses drugs on active hair follicles. Wound healing may be delayed. Long-term effects on the gonads may result in amenorrhoea and the inhibition of spermatogenesis.<br>Most antineoplastics are potentially mutagenic or teratogenic and coupled with the effects of prolonged immunosuppression may also be carcinogenic. |

| | | |
|---|---|---|
| **bortezomib** | **TOXICITY** | **IRRITATION** |
| | Not Available | Not Available |

**Continued...**

| | |
|---|---|
| ***Legend:*** | *1. Value obtained from Europe ECHA Registered Substances - Acute toxicity 2.* Value obtained from manufacturer's SDS. Unless otherwise specified data extracted from RTECS - Register of Toxic Effect of chemical Substances* |

| | |
|---|---|
| **BORTEZOMIB** | No significant acute toxicological data identified in literature search.<br>Treatment related side effects include fatigue, dizziness, syncope, orthostatic/ postural hypotension, vomiting and diarrhoea.<br>Bortezomib is associated with peripheral neuropathy (tingling, numbness, pain or burning felling in the hands or feet or weakness in the arms or legs) in 30% of patients; occasionally, it can be painful. This can be worse in patients with pre-existing neuropathy. In addition, myelosuppression as neutropenia and thrombocytopenia can also occur and be dose limiting. However, relative to other treatment options for patients with advanced disease (eg, bone marrow transplantation), these side effects are mild. Bortezomib is associated with a high rate of shingles (reactivation of the chicken pox virus in a nerve distribution, also referred to as zoster).<br>GI effects and asthenia are the most common adverse events.<br>Cardiovascular safety pharmacology studies in monkeys show that lethal IV doses are associated with decreases in blood pressure, increases in heart rate, increases in contractility, and ultimately terminal hypotension. In monkeys, doses of 3.0 mg/m2 and greater (approximately twice the recommended clinical dose) resulted in progressive hypotension starting at 1 hour and progressing to death by 12 to 14 hours following drug administration.<br>Bortezomib is a reversible inhibitor of the chymotrypsin-like activity of the 26S proteasome in mammalian cells. The 26S proteasome is a large protein complex that degrades ubiquitinated proteins. The active site of the proteasome has chymotrypsin-like, trypsin-like, and postglutamyl peptide hydrolysis activity. The 26S proteasome degrades various proteins critical to cancer cell survival, such as cyclins, tumor suppressors, BCL-2, and cyclin-dependent kinase inhibitors. Inhibition of these degradations sensitises cells to apoptosis. Bortezomib is a potent inhibitor of 26S proteasome, which sensitises activity in dividing multiple myeloma and leukemic cells, thus inducing apoptosis. In addition, bortezomib appears to increase the sensitivity of cancer cells to traditional anticancer agents (e.g., gemcitabine, cisplatin, paclitaxel, irinotecan, and radiation). |

| | | | |
|---|---|---|---|
| **Acute Toxicity** | ⊘ | **Carcinogenicity** | ⊘ |
| **Skin Irritation/Corrosion** | ⊘ | **Reproductivity** | ✔ |
| **Serious Eye Damage/Irritation** | ⊘ | **STOT - Single Exposure** | ⊘ |
| **Respiratory or Skin sensitisation** | ⊘ | **STOT - Repeated Exposure** | ⊘ |
| **Mutagenicity** | ⊘ | **Aspiration Hazard** | ⊘ |

***Legend:*** ✘ *– Data available but does not fill the criteria for classification*
✔ *– Data required to make classification available*
⊘ *– Data Not Available to make classification*

## SECTION 12 ECOLOGICAL INFORMATION

### Toxicity

| Ingredient | Endpoint | Test Duration (hr) | Species | Value | Source |
|---|---|---|---|---|---|
| **bortezomib** | EC50 | 384 | Crustacea | 15.653mg/L | 3 |
| **bortezomib** | EC50 | 96 | Algae or other aquatic plants | 190.814mg/L | 3 |
| **bortezomib** | LC50 | 96 | Fish | 65.254mg/L | 3 |
| ***Legend:*** | *Extracted from 1. IUCLID Toxicity Data 2. Europe ECHA Registered Substances - Ecotoxicological Information - Aquatic Toxicity 3. EPIWIN Suite V3.12 - Aquatic Toxicity Data (Estimated) 4. US EPA, Ecotox database - Aquatic Toxicity Data 5. ECETOC Aquatic Hazard Assessment Data 6. NITE (Japan) - Bioconcentration Data 7. METI (Japan) - Bioconcentration Data 8. Vendor Data* | | | | |

For antineoplastics:
**Ecotoxicity:**
Because antineoplastics are genotoxic, mutagenic and carcinogenic concerns are warranted for their potential effect in the environment. There are a number of known mammalian toxic and nausea effects associated with antineoplastic treatment, which could indicate that similar effects, might be expected in non-target mammals, and possibly also in non-target species other than mammals.
Total dosage over a whole therapy protocol is approximately 150 mg /kg body weight. Approximately 14-53% of the administered pharmaceutical is excreted unmetabolised into urine.
Antineoplastics as a class of drugs are of potential concern for environmental impacts, not just for their acute toxicity but perhaps more for their ability to effect subtle genetic changes, the cumulative impact of which over time can lead to more profound ecologic change. Hospitals are the major source of genotoxic drugs. publicly-owned waste-water treatment works (POTWs) that service hospitals, especially multiple hospitals, are likely candidates for releasing these chemicals into surface waters.
Antineoplastics are highly [geno]toxic compounds, primarily from hospitals, with poor removal from sewage treatment plants (STWs). Antineoplastic agents, antitumour agents primarily used only within hospitals for chemotherapy, are found sporadically and in a range of concentrations, probably because only small amounts are introduced to STWs via domestic sewage because of their long-lived physiologic retention.
These compounds act as nonspecific alkylating agents (i.e., specific receptors are not involved) and therefore have the potential to act as either acute or long-felt stressors (mutagens carcinogens/ teratogens/ embryotoxins) in any organism.
Using well-established QSAR modelling techniques almost 1/5 of the commonly used antineoplastics were predicted to be very toxic to algae, and close to 1/3 were predicted to be non-toxic to plants. A third of the compounds were predicted to be very toxic to daphnids, and almost half were predicted to be non-toxic to daphnids. Slightly more than 1/5 were predicted to be very toxic to fish, and 47% were predicted to be non-toxic to fish.
**DO NOT** discharge into sewer or waterways.

### Persistence and degradability

| Ingredient | Persistence: Water/Soil | Persistence: Air |
|---|---|---|
| bortezomib | HIGH | HIGH |

### Bioaccumulative potential

| Ingredient | Bioaccumulation |
|---|---|
| bortezomib | LOW (LogKOW = 1.995) |

### Mobility in soil

| Ingredient | Mobility |
|---|---|
| bortezomib | LOW (KOC = 31930) |

**Continued...**

## SECTION 13 DISPOSAL CONSIDERATIONS

### Waste treatment methods

| | |
|---|---|
| **Product / Packaging disposal** | ▸ Antineoplastic (cytotoxic) wastes must be packed directly, ready for incineration, into colour-coded, secure, labelled, leak-proof containers sufficiently robust to withstand handling without breaking, bursting or leaking.<br>▸ Containers of special design are available for particular needs (such as disposal of sharps) and should be used.<br>▸ Once filled and closed, such containers must never be re-opened.<br>▸ Immediate containers must bear a nationally accepted symbol or device depicting cytotoxic substances and be labelled with the words: CYTOTOXIC WASTE - INCINERATE in a style of lettering approved by the national/ state authority.<br>▸ Where policies and procedures permit the merging of cytotoxic wastes with medical waste in an outer container used for medical waste, cytotoxic waste must first be placed in identifiable colour-coded/ labelled cytotoxic containers prior to merging.<br>▸ Management procedures must ensure that merged medical and cytotoxic waste is subjected to the incineration requirements appropriate for the total destruction of the cytotoxic waste.<br>**WASTE STORAGE OF CYTOTOXIC WASTES**<br>For the storage of cytotoxic waste, segregated or merged with medical waste, provide:<br>▸ special storage areas with adequate lighting.<br>▸ waste security and restriction of access to authorised persons.<br>▸ storage areas designed to facilitate easy routine cleaning and maintenance to hygienic standards, or post-spill decontamination.<br>▸ storage of cytotoxic waste in standard, identifying bins or other appropriate containers.<br>**COLLECTION OF CYTOTOXIC WASTES**<br>▸ Procedures for the collection of cytotoxic wastes, which are compatible with existing operational needs, and which protect workers, other people and the environment, must be developed.<br>▸ Waste must be removed from the site by contractors whose workers have been instructed in the protective methods to be used against the hazards involved, and who comply with the safe work practices established by internal and/or national/ state policies. Contractors must instruct, train and direct their personnel in the safe and legal handling of cytotoxic wastes. Contractor's personnel should observe the operating procedures of the waste-generator.<br>▸ Transport of cytotoxic wastes, through the community, must comply with the appropriate national/ state codes.<br>**DESTRUCTION OF CYTOTOXIC WASTES**<br>▸ Destruction of cytotoxic wastes should be carried out in multi-chambered incinerators, licenced for this purpose, operating at 1100 deg. C. or more, with a residence time of at least 1 second.<br>▸ Operators must be trained in handling procedures and hazards involved with handling the waste.<br>▸ Waste which arrives at the incinerator inappropriately packaged should **NOT** be returned to the waste generator. An authorised representative of the waste generator must attend the incinerator site to rectify the situation.<br>Legislation addressing waste disposal requirements may differ by country, state and/ or territory. Each user must refer to laws operating in their area. In some areas, certain wastes must be tracked.<br>A Hierarchy of Controls seems to be common - the user should investigate:<br>▸ Reduction<br>▸ Reuse<br>▸ Recycling<br>▸ Disposal (if all else fails)<br>This material may be recycled if unused, or if it has not been contaminated so as to make it unsuitable for its intended use. Shelf life considerations should also be applied in making decisions of this type. Note that properties of a material may change in use, and recycling or reuse may not always be appropriate. In most instances the supplier of the material should be consulted.<br>▸ **DO NOT** allow wash water from cleaning or process equipment to enter drains.<br>▸ It may be necessary to collect all wash water for treatment before disposal.<br>▸ In all cases disposal to sewer may be subject to local laws and regulations and these should be considered first.<br>▸ Where in doubt contact the responsible authority. |

## SECTION 14 TRANSPORT INFORMATION

### Labels Required

| | |
|---|---|
| **Marine Pollutant** | NO |

**Land transport (UN): NOT REGULATED FOR TRANSPORT OF DANGEROUS GOODS**

**Air transport (ICAO-IATA / DGR): NOT REGULATED FOR TRANSPORT OF DANGEROUS GOODS**

**Sea transport (IMDG-Code / GGVSee): NOT REGULATED FOR TRANSPORT OF DANGEROUS GOODS**

### Transport in bulk according to Annex II of MARPOL and the IBC code

Not Applicable

## SECTION 15 REGULATORY INFORMATION

### Safety, health and environmental regulations / legislation specific for the substance or mixture

**BORTEZOMIB(179324-69-7) IS FOUND ON THE FOLLOWING REGULATORY LISTS**

Not Applicable

| National Inventory | Status |
|---|---|
| Australia - AICS | N (bortezomib) |
| Canada - DSL | N (bortezomib) |
| Canada - NDSL | N (bortezomib) |
| China - IECSC | N (bortezomib) |
| Europe - EINEC / ELINCS / NLP | N (bortezomib) |
| Japan - ENCS | N (bortezomib) |
| Korea - KECI | N (bortezomib) |

**Continued...**

| | |
|---|---|
| New Zealand - NZIoC | N (bortezomib) |
| Philippines - PICCS | N (bortezomib) |
| USA - TSCA | N (bortezomib) |
| ***Legend:*** | *Y = All ingredients are on the inventory*<br>*N = Not determined or one or more ingredients are not on the inventory and are not exempt from listing(see specific ingredients in brackets)* |

## SECTION 16 OTHER INFORMATION

### Other information

Classification of the preparation and its individual components has drawn on official and authoritative sources as well as independent review by the Chemwatch Classification committee using available literature references.
A list of reference resources used to assist the committee may be found at:
www.chemwatch.net

The SDS is a Hazard Communication tool and should be used to assist in the Risk Assessment. Many factors determine whether the reported Hazards are Risks in the workplace or other settings. Risks may be determined by reference to Exposures Scenarios. Scale of use, frequency of use and current or available engineering controls must be considered.

### Definitions and abbreviations

PC—TWA: Permissible Concentration-Time Weighted Average
PC—STEL: Permissible Concentration-Short Term Exposure Limit
IARC: International Agency for Research on Cancer
ACGIH: American Conference of Governmental Industrial Hygienists
STEL: Short Term Exposure Limit
TEEL: Temporary Emergency Exposure Limit。
IDLH: Immediately Dangerous to Life or Health Concentrations
OSF: Odour Safety Factor
NOAEL :No Observed Adverse Effect Level
LOAEL: Lowest Observed Adverse Effect Level
TLV: Threshold Limit Value
LOD: Limit Of Detection
OTV: Odour Threshold Value
BCF: BioConcentration Factors
BEI: Biological Exposure Index