

Ilium Xylazil-100 Analgesic, Sedative and Muscle Relaxant Injection

Troy Laboratories Pty Ltd

Chemwatch Hazard Alert Code: 2

Chemwatch: 5398-35

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Safety Data Sheet according to Work Health and Safety Regulations (Hazardous Chemicals) 2023 and ADG requirements

L.GHS.AUS.EN.E

SECTION 1 Identification of the substance / mixture and of the company / undertaking

Product Identifier

Product name	Ilium Xylazil-100 Analgesic, Sedative and Muscle Relaxant Injection
Chemical Name	Not Applicable
Synonyms	APVMA number: 38654
Chemical formula	Not Applicable
Other means of identification	Not Available

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

Relevant identified uses	An analgesic, sedative and muscle relaxant for use in horses. To be used as directed on product label.
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Details of the manufacturer or supplier of the safety data sheet

Registered company name	Troy Laboratories Pty Ltd
Address	37 Glendenning Road Glendenning NSW 2761 Australia
Telephone	02 8808 3600
Fax	02 9677 9300
Website	www.Troylab.com.au
Email	admin@troylab.com.au

Emergency telephone number

Association / Organisation	Ixom Emergency Response Service
Emergency telephone number(s)	1800 033 111 (24 hours)
Other emergency telephone number(s)	Not Available

SECTION 2 Hazards identification

Classification of the substance or mixture

Poisons Schedule	S4
Classification ^[1]	Acute Toxicity (Oral) Category 4, Skin Corrosion/Irritation Category 2, Sensitisation (Skin) Category 1
Legend:	1. Classified by Chemwatch; 2. Classification drawn from HCIS; 3. Classification drawn from Regulation (EU) No 1272/2008 - Annex VI

Label elements

Hazard pictogram(s)	
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Signal word	Warning
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Hazard statement(s)

H302	Harmful if swallowed.
H315	Causes skin irritation.
H317	May cause an allergic skin reaction.

Precautionary statement(s) Prevention

P280	Wear protective gloves and protective clothing.
P261	Avoid breathing mist/vapours/spray.
P264	Wash all exposed external body areas thoroughly after handling.
P270	Do not eat, drink or smoke when using this product.
P272	Contaminated work clothing should not be allowed out of the workplace.

Precautionary statement(s) Response

P302+P352	IF ON SKIN: Wash with plenty of water.
P333+P313	If skin irritation or rash occurs: Get medical advice/attention.
P362+P364	Take off contaminated clothing and wash it before reuse.
P301+P312	IF SWALLOWED: Call a POISON CENTER/doctor/physician/first aider if you feel unwell.
P330	Rinse mouth.

Precautionary statement(s) Storage

Not Applicable

Precautionary statement(s) Disposal

P501	Dispose of contents/container to authorised hazardous or special waste collection point in accordance with any local regulation.
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SECTION 3 Composition / information on ingredients

Substances

See section below for composition of Mixtures

Mixtures

CAS No	%[weight]	Name
23076-35-9	10-30	<u>xylazine hydrochloride</u>
6132-04-3	1-10	<u>sodium citrate</u>
100-51-6	1-10	<u>benzyl alcohol</u>
Not Available	balance	Ingredients determined not to be hazardous

Legend: 1. Classified by Chemwatch; 2. Classification drawn from HCIS; 3. Classification drawn from Regulation (EU) No 1272/2008 - Annex VI; 4. Classification drawn from C&L; * EU IOELVs available

SECTION 4 First aid measures

Description of first aid measures

Eye Contact	<p>If this product comes in contact with eyes:</p> <ul style="list-style-type: none"> ▶ Wash out immediately with water. ▶ If irritation continues, seek medical attention. ▶ Removal of contact lenses after an eye injury should only be undertaken by skilled personnel.
Skin Contact	<p>If skin contact occurs:</p> <ul style="list-style-type: none"> ▶ Immediately remove all contaminated clothing, including footwear. ▶ Flush skin and hair with running water (and soap if available). ▶ Seek medical attention in event of irritation.
Inhalation	<ul style="list-style-type: none"> ▶ If fumes, aerosols or combustion products are inhaled remove from contaminated area. ▶ Other measures are usually unnecessary.
Ingestion	<ul style="list-style-type: none"> ▶ For advice, contact a Poisons Information Centre or a doctor at once. ▶ Urgent hospital treatment is likely to be needed. ▶ If swallowed do NOT induce vomiting. ▶ If vomiting occurs, lean patient forward or place on left side (head-down position, if possible) to maintain open airway and prevent aspiration. ▶ Observe the patient carefully. ▶ Never give liquid to a person showing signs of being sleepy or with reduced awareness; i.e. becoming unconscious.

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- ▶ Give water to rinse out mouth, then provide liquid slowly and as much as casualty can comfortably drink.
- ▶ Transport to hospital or doctor without delay.

Indication of any immediate medical attention and special treatment needed

Treat symptomatically.

SECTION 5 Firefighting measures

Extinguishing media

The product contains a substantial proportion of water, therefore there are no restrictions on the type of extinguishing media which may be used. Choice of extinguishing media should take into account surrounding areas.

Though the material is non-combustible, evaporation of water from the mixture, caused by the heat of nearby fire, may produce floating layers of combustible substances.

In such an event consider:

- ▶ foam.
- ▶ dry chemical powder.
- ▶ carbon dioxide.

Special hazards arising from the substrate or mixture

Fire Incompatibility	None known.
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Advice for firefighters

Fire Fighting	<ul style="list-style-type: none"> ▶ Alert Fire Brigade and tell them location and nature of hazard. ▶ Wear breathing apparatus plus protective gloves in the event of a fire. ▶ Prevent, by any means available, spillage from entering drains or water courses. ▶ Use fire fighting procedures suitable for surrounding area. ▶ DO NOT approach containers suspected to be hot. ▶ Cool fire exposed containers with water spray from a protected location. ▶ If safe to do so, remove containers from path of fire. ▶ Equipment should be thoroughly decontaminated after use.
Fire/Explosion Hazard	<ul style="list-style-type: none"> ▶ The material is not readily combustible under normal conditions. ▶ However, it will break down under fire conditions and the organic component may burn. ▶ Not considered to be a significant fire risk. ▶ Heat may cause expansion or decomposition with violent rupture of containers. ▶ Decomposes on heating and may produce toxic fumes of carbon monoxide (CO). ▶ May emit acrid smoke. <p>Decomposes on heating and produces toxic fumes of: carbon dioxide (CO₂) hydrogen chloride phosgene nitrogen oxides (NO_x) sulfur oxides (SO_x) other pyrolysis products typical of burning organic material. May emit poisonous fumes.</p>
HAZCHEM	Not Applicable

SECTION 6 Accidental release measures

Personal precautions, protective equipment and emergency procedures

See section 8

Environmental precautions

See section 12

Methods and material for containment and cleaning up

Minor Spills	<ul style="list-style-type: none"> ▶ Clean up all spills immediately. ▶ Avoid breathing vapours and contact with skin and eyes. ▶ Control personal contact with the substance, by using protective equipment. ▶ Contain and absorb spill with sand, earth, inert material or vermiculite. ▶ Wipe up. ▶ Place in a suitable, labelled container for waste disposal.
Major Spills	<p>Moderate hazard.</p> <ul style="list-style-type: none"> ▶ Clear area of personnel and move upwind. ▶ Alert Fire Brigade and tell them location and nature of hazard. ▶ Wear breathing apparatus plus protective gloves. ▶ Prevent, by any means available, spillage from entering drains or water course. ▶ Stop leak if safe to do so.

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- ▶ Contain spill with sand, earth or vermiculite.
- ▶ Collect recoverable product into labelled containers for recycling.
- ▶ Neutralise/decontaminate residue (see Section 13 for specific agent).
- ▶ Collect solid residues and seal in labelled drums for disposal.
- ▶ Wash area and prevent runoff into drains.
- ▶ After clean up operations, decontaminate and launder all protective clothing and equipment before storing and re-using.
- ▶ 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

Safe handling	<ul style="list-style-type: none"> ▶ Avoid all personal contact, including inhalation. ▶ Wear protective clothing when risk of exposure occurs. ▶ Use in a well-ventilated area. ▶ Prevent concentration in hollows and sumps. ▶ DO NOT enter confined spaces until atmosphere has been checked. ▶ DO NOT allow material to contact humans, exposed food or food utensils. ▶ Avoid contact with incompatible materials. ▶ When handling, DO NOT eat, drink or smoke. ▶ Keep containers securely sealed when not in use. ▶ Avoid physical damage to containers. ▶ Always wash hands with soap and water after handling. ▶ Work clothes should be laundered separately. Launder contaminated clothing before re-use. ▶ Use good occupational work practice. ▶ Observe manufacturer's storage and handling recommendations contained within this SDS. ▶ Atmosphere should be regularly checked against established exposure standards to ensure safe working conditions are maintained.
Other information	<ul style="list-style-type: none"> ▶ Store in original containers. ▶ Keep containers securely sealed. ▶ Store in a cool, dry, well-ventilated area. ▶ Store away from incompatible materials and foodstuff containers. ▶ Protect containers against physical damage and check regularly for leaks. ▶ Observe manufacturer's storage and handling recommendations contained within this SDS.

Conditions for safe storage, including any incompatibilities

Suitable container	<ul style="list-style-type: none"> ▶ Glass container is suitable for laboratory quantities ▶ Polyethylene or polypropylene container. ▶ Packing as recommended by manufacturer. ▶ Check all containers are clearly labelled and free from leaks.
Storage incompatibility	<ul style="list-style-type: none"> ▶ Avoid reaction with oxidising agents ▶ Avoid strong acids, bases.

SECTION 8 Exposure controls / personal protection

Control parameters

Occupational Exposure Limits (OEL)

INGREDIENT DATA

Not Available

Ingredient	Original IDLH	Revised IDLH
xylazine hydrochloride	Not Available	Not Available
sodium citrate	Not Available	Not Available
benzyl alcohol	Not Available	Not Available

MATERIAL DATA

Exposure controls

Appropriate engineering controls	<p>Enclosed local exhaust ventilation is required at points of dust, fume or vapour generation. HEPA terminated local exhaust ventilation should be considered at point of generation of dust, fumes or vapours. Barrier protection or laminar flow cabinets should be considered for laboratory scale handling. A fume hood or vented balance enclosure is recommended for weighing/ transferring quantities exceeding 500 mg. When handling quantities up to 500 gram in either a standard laboratory with general dilution ventilation (e.g. 6-12 air changes per hour) is preferred. Quantities up to 1 kilogram may require a designated laboratory using fume hood, biological safety cabinet, or approved vented enclosures. Quantities exceeding 1 kilogram should be handled in a designated laboratory or containment laboratory using appropriate barrier/ containment technology. Manufacturing and pilot plant operations require barrier/ containment and direct coupling technologies.</p>
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Barrier/ containment technology and direct coupling (totally enclosed processes that create a barrier between the equipment and the room) typically use double or split butterfly valves and hybrid unidirectional airflow/ local exhaust ventilation solutions (e.g. powder containment booths). Glove bags, isolator glove box systems are optional. HEPA filtration of exhaust from dry product handling areas is required.

Fume-hoods and other open-face containment devices are acceptable when face velocities of at least 1 m/s (200 feet/minute) are achieved. Partitions, barriers, and other partial containment technologies are required to prevent migration of the material to uncontrolled areas. For non-routine emergencies maximum local and general exhaust are necessary. Air contaminants generated in the workplace possess varying "escape" velocities which, in turn, determine the "capture velocities" of fresh circulating air required to effectively remove the contaminant.

Type of Contaminant:	Air Speed:
solvent, vapours, etc. evaporating from tank (in still air)	0.25-0.5 m/s (50-100 f/min.)
aerosols, fumes from pouring operations, intermittent container filling, low speed conveyer transfers (released at low velocity into zone of active generation)	0.5-1 m/s (100-200 f/min.)
direct spray, drum filling, conveyer loading, crusher dusts, gas discharge (active generation into zone of rapid air motion)	1-2.5 m/s (200-500 f/min.)

Within each range the appropriate value depends on:

Lower end of the range	Upper end of the range
1: Room air currents minimal or favourable to capture	1: Disturbing room air currents
2: Contaminants of low toxicity or of nuisance value only.	2: Contaminants of high toxicity
3: Intermittent, low production.	3: High production, heavy use
4: Large hood or large air mass in motion	4: Small hood-local control only

Simple theory shows that air velocity falls rapidly with distance away from the opening of a simple extraction pipe. Velocity generally decreases with the square of distance from the extraction point (in simple cases). Therefore the air speed at the extraction point should be adjusted, accordingly, after reference to distance from the contaminating source. The air velocity at the extraction fan, for example, should be a minimum of 1-2.5 m/s (200-500 f/min.) for extraction of gases discharged 2 meters distant from the extraction point. Other mechanical considerations, producing performance deficits within the extraction apparatus, make it essential that theoretical air velocities are multiplied by factors of 10 or more when extraction systems are installed or used.

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.

The following protective devices are recommended where exposures exceed the recommended exposure control guidelines by factors of:

- 10; high efficiency particulate (HEPA) filters or cartridges
- 10-25; loose-fitting (Tyvek or helmet type) HEPA powered-air purifying respirator.
- 25-50; a full face-piece negative pressure respirator with HEPA filters
- 50-100; tight-fitting, full face-piece HEPA PAPR
- 100-1000; a hood-shroud HEPA PAPR or full face-piece supplied air respirator operated in pressure demand or other positive pressure mode.

Individual protection measures, such as personal protective equipment



Eye and face protection

When handling very small quantities of the material eye protection may not be required.

For laboratory, larger scale or bulk handling or where regular exposure in an occupational setting occurs:

- ▶ Chemical goggles. [AS/NZS 1337.1, EN166 or national equivalent]
- ▶ Face shield. Full face shield may be required for supplementary but never for primary protection of eyes.
- ▶ 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].

Skin protection

See Hand protection below

Hands/feet protection

- ▶ Rubber gloves (nitrile or low-protein, powder-free latex, latex/ nitrile). Employees allergic to latex gloves should use nitrile gloves in preference.
- ▶ Double gloving should be considered.
- ▶ PVC gloves.
- ▶ Change gloves frequently and when contaminated, punctured or torn.
- ▶ Wash hands immediately after removing gloves.
- ▶ Protective shoe covers. [AS/NZS 2210]
- ▶ Head covering.

Body protection

See Other protection below

Other protection

- ▶ For quantities up to 500 grams a laboratory coat may be suitable.
- ▶ 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.

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- ▶ For quantities over 1 kilogram and manufacturing operations, wear disposable coverall of low permeability and disposable shoe covers.
- ▶ For manufacturing operations, air-supplied full body suits may be required for the provision of advanced respiratory protection.
- ▶ Eye wash unit.
- ▶ Ensure there is ready access to an emergency shower.
- ▶ For Emergencies: Vinyl suit

Recommended material(s)

GLOVE SELECTION INDEX

Glove selection is based on a modified presentation of the:

"Forsberg Clothing Performance Index".

The effect(s) of the following substance(s) are taken into account in the **computer-generated** selection:

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Material	CPI
BUTYL	C
NATURAL RUBBER	C
NATURAL+NEOPRENE	C
NEOPRENE	C
NITRILE	C
PVA	C
VITON	C

* CPI - Chemwatch Performance Index

A: Best Selection

B: Satisfactory; may degrade after 4 hours continuous immersion

C: Poor to Dangerous Choice for other than short term immersion

NOTE: As a series of factors will influence the actual performance of the glove, a final selection must be based on detailed observation. -

* Where the glove is to be used on a short term, casual or infrequent basis, factors such as "feel" or convenience (e.g. disposability), may dictate a choice of gloves which might otherwise be unsuitable following long-term or frequent use. A qualified practitioner should be consulted.

Respiratory protection

Type A Filter of sufficient capacity. (AS/NZS 1716 & 1715, EN 143:2000 & 149:2001, ANSI Z88 or national equivalent)

Selection of the Class and Type of respirator will depend upon the level of breathing zone contaminant and the chemical nature of the contaminant.

Protection Factors (defined as the ratio of contaminant outside and inside the mask) may also be important.

Required minimum protection factor	Maximum gas/vapour concentration present in air p.p.m. (by volume)	Half-face Respirator	Full-Face Respirator
up to 10	1000	A-AUS / Class1	-
up to 50	1000	-	A-AUS / Class 1
up to 50	5000	Airline *	-
up to 100	5000	-	A-2
up to 100	10000	-	A-3
100+			Airline**

* - Continuous Flow ** - Continuous-flow or positive pressure demand

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)

- ▶ Cartridge respirators should never be used for emergency ingress or in areas of unknown vapour concentrations or oxygen content.
- ▶ The wearer must be warned to leave the contaminated area immediately on detecting any odours through the respirator. The odour may indicate that the mask is not functioning properly, that the vapour concentration is too high, or that the mask is not properly fitted. Because of these limitations, only restricted use of cartridge respirators is considered appropriate.
- ▶ Cartridge performance is affected by humidity. Cartridges should be changed after 2 hr of continuous use unless it is determined that the humidity is less than 75%, in which case, cartridges can be used for 4 hr. Used cartridges should be discarded daily, regardless of the length of time used

SECTION 9 Physical and chemical properties

Information on basic physical and chemical properties

Appearance	Clear colourless liquid with very faint odour; mixes with water.		
Physical state	Liquid	Relative density (Water = 1)	1.025
Odour	Not Available	Partition coefficient n-octanol / water	Not Available
Odour threshold	Not Available	Auto-ignition temperature (°C)	Not Applicable
pH (as supplied)	4.5-5.5	Decomposition temperature (°C)	Not Available
Melting point / freezing point (°C)	~0	Viscosity (cSt)	Not Available
Initial boiling point and boiling range (°C)	~100	Molecular weight (g/mol)	Not Applicable
Flash point (°C)	Not Applicable	Taste	Not Available

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Evaporation rate	Not Available	Explosive properties	Not Available
Flammability	Not Applicable	Oxidising properties	Not Available
Upper Explosive Limit (%)	Not Applicable	Surface Tension (dyn/cm or mN/m)	Not Available
Lower Explosive Limit (%)	Not Applicable	Volatile Component (%vol)	Not Available
Vapour pressure (kPa)	2.37 @20C	Gas group	Not Available
Solubility in water	Miscible	pH as a solution (1%)	Not Available
Vapour density (Air = 1)	Not Available	VOC g/L	Not Available
Heat of Combustion (kJ/g)	Not Available	Ignition Distance (cm)	Not Available
Flame Height (cm)	Not Available	Flame Duration (s)	Not Available
Enclosed Space Ignition Time Equivalent (s/m3)	Not Available	Enclosed Space Ignition Deflagration Density (g/m3)	Not Available

SECTION 10 Stability and reactivity

Reactivity	See section 7
Chemical stability	<ul style="list-style-type: none"> ▶ Unstable in the presence of incompatible materials. ▶ Product is considered stable. ▶ 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

a) Acute Toxicity	There is sufficient evidence to classify this material as acutely toxic.
b) Skin Irritation/Corrosion	There is sufficient evidence to classify this material as skin corrosive or irritating.
c) Serious Eye Damage/Irritation	Based on available data, the classification criteria are not met.
d) Respiratory or Skin sensitisation	There is sufficient evidence to classify this material as sensitising to skin or the respiratory system
e) Mutagenicity	Based on available data, the classification criteria are not met.
f) Carcinogenicity	Based on available data, the classification criteria are not met.
g) Reproductivity	Based on available data, the classification criteria are not met.
h) STOT - Single Exposure	Based on available data, the classification criteria are not met.
i) STOT - Repeated Exposure	Based on available data, the classification criteria are not met.
j) Aspiration Hazard	Based on available data, the classification criteria are not met.

Inhaled	The material is not thought to produce adverse health effects or irritation of the respiratory tract (as classified by EC Directives using animal models). Nevertheless, good hygiene practice requires that exposure be kept to a minimum and that suitable control measures be used in an occupational setting. Not normally a hazard due to non-volatile nature of product
Ingestion	The material has NOT been classified by EC Directives or other classification systems as "harmful by ingestion". This is because of the lack of corroborating animal or human evidence. The material may still be damaging to the health of the individual, following ingestion, especially where pre-existing organ (e.g liver, kidney) damage is evident. Present definitions of harmful or toxic substances are generally based on doses producing mortality rather than those producing morbidity (disease, ill-health). Gastrointestinal tract discomfort may produce nausea and vomiting. In an occupational setting however, ingestion of insignificant quantities is not thought to be cause for concern.
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.
Eye	Although the liquid is not thought to be an irritant (as classified by EC Directives), direct contact with the eye may produce transient discomfort characterised by tearing or conjunctival redness (as with windburn).
Chronic	Practical experience shows that skin contact with the material is capable either of inducing a sensitisation reaction in a substantial number of individuals, and/or of producing a positive response in experimental animals.

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Substances that can cause occupational asthma (also known as asthmagens and respiratory sensitisers) can induce a state of specific airway hyper-responsiveness via an immunological, irritant or other mechanism. Once the airways have become hyper-responsive, further exposure to the substance, sometimes even to tiny quantities, may cause respiratory symptoms. These symptoms can range in severity from a runny nose to asthma. Not all workers who are exposed to a sensitiser will become hyper-responsive and it is impossible to identify in advance who are likely to become hyper-responsive.

Substances that can cause occupational asthma should be distinguished from substances which may trigger the symptoms of asthma in people with pre-existing air-way hyper-responsiveness. The latter substances are not classified as asthmagens or respiratory sensitisers

Wherever it is reasonably practicable, exposure to substances that can cause occupational asthma should be prevented. Where this is not possible the primary aim is to apply adequate standards of control to prevent workers from becoming hyper-responsive.

Activities giving rise to short-term peak concentrations should receive particular attention when risk management is being considered. Health surveillance is appropriate for all employees exposed or liable to be exposed to a substance which may cause occupational asthma and there should be appropriate consultation with an occupational health professional over the degree of risk and level of surveillance.

Limited evidence suggests that repeated or long-term occupational exposure may produce cumulative health effects involving organs or biochemical systems.

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	Not Available	Not Available
xylazine hydrochloride	TOXICITY	IRRITATION
	Oral (Rat) LD50: 130 mg/kg ^[2]	Not Available
sodium citrate	TOXICITY	IRRITATION
	dermal (rat) LD50: >2000 mg/kg ^[1]	Eye: no adverse effect observed (not irritating) ^[1]
	Oral (Mouse) LD50; 5000-6000 mg/kg ^[2]	Skin: no adverse effect observed (not irritating) ^[1]
benzyl alcohol	TOXICITY	IRRITATION
	Dermal (rabbit) LD50: 2000 mg/kg ^[2]	Eye (Rodent - rat): 0.1mL
	Inhalation (Rat) LC50: >4.178 mg/L4h ^[2]	Eye: adverse effect observed (irritating) ^[1]
	Oral (Rat) LD50: 1230 mg/kg ^[2]	Skin (Human - man): 16mg/48H - Mild
		Skin (Human): 1%/2D
		Skin (Mammal - pig): 100% - Moderate
		Skin (Rodent - rabbit): 100mg/24H - Moderate
		Skin: no adverse effect observed (not irritating) ^[1]
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	

**XYLAZINE
HYDROCHLORIDE**

results from early human clinical studies confirmed that xylazine has several central nervous system depressant effects.] Xylazine administration is used for sedation, anesthesia, muscle relaxation, and analgesia.] It causes a significant reduction in blood pressure and heart rate in healthy volunteers.[failed verification]] Xylazine was also studied for use in human beings, but due to hazardous side effects, including hypotension and bradycardia, it was not approved by the Food and Drug Administration (FDA) for human use. sedative and analgesic effects of xylazine are related to central nervous system depression. Xylazine's muscle relaxant The known doses of xylazine that produce toxicity and fatality in humans vary from 40 to 2400 mg.. Small doses may produce toxicity and larger doses may be survived with medical assistance.] Non-fatal blood or plasma concentration ranges from 0.03 to 4.6 mg/L] In fatalities, the blood concentration of xylazine ranges from trace to 16 mg/L.] It is reported that there is no defined safe or fatal concentration of xylazine because of the significant overlap between the non-fatal and postmortem blood concentrations of xylazine.. The sedative and analgesic effects of xylazine are related to central nervous system depression. Xylazine's muscle relaxant Xylazine overdose is usually fatal in humans. Because it is used as a drug adulterant, the symptoms caused by the drugs accompanying xylazine administration vary between individuals.. Side effects in animals include transient hypertension, hypotension, and respiratory depression..] Further, the decrease of tissue sensitivity to insulin leads to xylazine-induced hyperglycemia and a reduction of tissue glucose uptake and utilization.[14] The duration of effects in animals lasts up to 4 hours The most common side effects in humans associated with xylazine administration include bradycardia, respiratory depression, hypotension, transient hypertension secondary to vagus nerve stimulation, and other changes in cardiac output. Xylazine significantly decreases heart rate in animals that are not premedicated with medications that have anticholinergic effects] The decrease in heart rate directly impacts aortic flow. Bradycardia caused by xylazine administration is effectively prevented by administration of atropine or glycopyrrolate. Arrhythmias associated with xylazine includes other symptoms such as sinoatrial block, atrioventricular block, A-V dissociation, and sinus arrhythmia. Xylazine administration can lead to diabetes mellitus and hyperglycemia.. Other possible side effects that can occur are areflexia, asthenia, ataxia, blurred vision, disorientation, dizziness, drowsiness, dysarthria, dysmetria, fainting, hyporeflexia, slurred speech, somnolence, staggering, coma, apnea, shallow breathing, sleepiness, premature ventricular contraction, tachycardia, miosis, and dry mouth. Rarely, hypotonia, dry mouth, urinary incontinence and nonspecific electrocardiographic ST segment changes occur. It has been reported that the duration of symptoms after human overdose is 8 to 72 hours. Further research is necessary to categorize the side effects that occur when xylazine is used in conjunction with heroin and cocaine. Chronic use is reported to be associated with physical deterioration, dependence, abscesses, and skin ulceration, which can be physically

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debilitating and painful. Hypertension followed by hypotension, bradycardia, and respiratory depression lower tissue oxygenation in the skin. Thus, chronic use of xylazine can progress the skin oxygenation deficit, leading to severe skin ulceration. Lower skin oxygenation is associated with impaired healing of wounds and a higher chance of infection. The ulcers may have a characteristic odor and ooze pus. In severe cases, amputations must be performed on the affected extremities. Xylazine is a potent α_2 adrenergic agonist. When xylazine and other α_2 adrenergic receptor agonists are administered, they distribute throughout the body within 30 to 40 minutes.[15] Due to xylazine's highly lipophilic nature, xylazine directly stimulates central α_2 receptors as well as peripheral α -adrenoceptors in a variety of tissues. As an agonist, xylazine leads to a decrease in neurotransmission of norepinephrine and dopamine in the central nervous system. It does so by mimicking norepinephrine in binding to presynaptic surface autoreceptors, which leads to feedback inhibition of norepinephrine. Xylazine also serves as a transport inhibitor by suppressing norepinephrine transport function through competitive inhibition of substrate transport. Accordingly, xylazine significantly increases K_m and does not affect V_{max} . This likely occurs by direct interaction on an area that overlaps with the antidepressant binding site. For example, xylazine and clonidine suppress uptake of MIBG, a norepinephrine analog, in neuroblastoma cells. Xylazine has varying affinities for cholinergic, serotonergic, dopaminergic, α_1 adrenergic, H₂-histaminergic and opiate receptors. Its chemical structure closely resembles the phenothiazines, tricyclic antidepressants, and clonidine.

α -Adrenergic receptors have actions in common, but also individual effects. Common (or still receptor unspecified) actions include:

- vasoconstriction
- decreased motility of smooth muscle in gastrointestinal tract

Subtype unspecific α agonists can be used to treat rhinitis (they decrease mucus secretion). Subtype unspecific α antagonists can be used to treat pheochromocytoma (they decrease vasoconstriction caused by norepinephrine).

α -agonist toxicity may occur accidentally or intentionally. Toxicity is often due to intentional overdose and accidental pediatric ingestion. Overdoses can occur after ingestion of pills, skin patches, or via self-administered medication pumps that may be misused or malfunctioning. Chronic and accidental overdose can occur in situations involving chronic pain, with use of oral extended-release and transdermal formulations. Pharmacy dosing and compounding errors have also occurred, which is of particular concern for pediatric toxicity. In addition, drug-drug interactions may occur.

α -adrenergic agonist toxicity is due to a broad group of pharmaceutical agents known as α agonists, which can be further broken down into central α_2 agonists and peripheral α_1 agonists. Stimulation of central α_2 receptors causes decreased secretion of catecholamines through a negative feedback mechanism. Stimulation of peripheral α_1 receptors primarily increases blood pressure via induced vasoconstriction. α -adrenergic agonist toxicity is of primary concern with α_2 adrenergic agonist xenobiotics through the resulting depletion of catecholamines associated with these agents; however, there are many topical α_1 agonists that when misused cause similar toxicity.

The primary mechanism of toxicity of α agonists is through central α_2 agonism. Central α_2 agonist toxicity may occur from an acute or nonacute overdose of central α_2 agonists or misuse of topical α_1 agonists, which when ingested, stimulate α_2 receptors. In overdose, an overall depletion of catecholamines occurs, leading to central nervous system depression, along with bradycardia and hypotension. Other clinical findings can include miosis, hypothermia, and possible respiratory depression. Paradoxically, in overdose, there is also transient stimulation of peripheral α_1 receptors and post-synaptic α_2 receptors, causing brief catecholamine release, which leads to an early, transient hypertension. Symptomatology is not necessarily dose-dependent.

The primary mechanism of action of α_2 agonists is stimulation of presynaptic α_2 receptors in the central nervous system, activating inhibitory neurons which lead to a reduction in sympathetic output via a negative feedback mechanism. This causes an overall decrease in the secretion of the catecholamine, norepinephrine, which is beneficial for the desired therapeutic effects of decreased blood pressure and heart rate.

The substance exhibits effects on the adrenergic receptors

The adverse effects seen with adrenergic drugs are broad. The most common side effects are changes in heart rate and blood pressure.

Non-selective binding to the adrenergic receptors can cause different side effects that vary based on the specific agent as well as the dosage. The common non-selective agonists are norepinephrine, epinephrine, and isoproterenol (isoprenaline). Common side effects are tachycardia, hypertension, arrhythmias, palpitations, and anxiety. Norepinephrine is less likely to cause arrhythmias than some of the other pressor medications, probably because it is more α_1 receptor-selective as compared with the β_1 receptor. [

Adrenergic receptors all have drug antagonists. α -blockers are not generally indicated for the treatment of α -agonist overdoses. β -blockers may be used to treat adverse effects arising from adrenergic receptor agonists acutely. β -blockers can treat tachycardia and hypertension that may occur from vasopressors. Toxicity should be monitored in the pediatric population when using β_2 agonists as they can increase concentrations of liver aminotransferase.

Many cells have these receptors, and the binding of a catecholamine to the receptor will generally stimulate the sympathetic nervous system (SNS). SNS is responsible for the fight-or-flight response, which is triggered for example by exercise or fear causing situations. This response dilates pupils, increases heart rate, mobilizes energy, and diverts blood flow from non-essential organs to skeletal muscle. These effects together tend to increase physical performance momentarily.

High catecholamine levels in blood are associated with stress, which can be induced from psychological reactions or environmental stressors such as elevated sound levels, intense light, or low blood sugar levels.

Extremely high levels of catecholamines (also known as catecholamine toxicity) can occur in central nervous system trauma due to stimulation and/or damage of nuclei in the brainstem, in particular those nuclei affecting the sympathetic nervous system. In emergency medicine, this occurrence is widely known as catecholamine dump.

Extremely high levels of catecholamine can also be caused by neuroendocrine tumours in the adrenal medulla, a treatable condition known as pheochromocytoma.

High levels of catecholamines can also be caused by monoamine oxidase A (MAO-A) deficiency. As MAO-A is one of the enzymes responsible for degradation of these neurotransmitters, its deficiency increases the bioavailability of these neurotransmitters considerably. It occurs in the absence of pheochromocytoma, neuroendocrine tumours, and carcinoid syndrome, but it looks similar to carcinoid syndrome such as facial flushing and aggression.

The acute porphyria's can cause elevated catecholamines

Epinephrine (adrenaline) reacts with both α - and β -adrenoreceptors, causing vasoconstriction and vasodilation, respectively. Although α receptors are less sensitive to epinephrine, when activated at pharmacologic doses, they override the vasodilation mediated by β -adrenoreceptors because there are more peripheral α_1 receptors than β -adrenoreceptors. The result is that high levels of circulating epinephrine cause vasoconstriction. However, the opposite is true in the coronary arteries, where β_2 response is greater than that of α_1 , resulting in overall dilation with increased sympathetic stimulation. At lower levels of circulating epinephrine (physiologic epinephrine secretion), β -adrenoreceptor stimulation

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dominates since epinephrine has a higher affinity for the beta2 adrenoceptor than the alpha1 adrenoceptor, producing vasodilation followed by decrease of peripheral vascular resistance.

The adrenergic receptors or adrenoceptors are a class of G protein-coupled receptors that are targets of many catecholamines like norepinephrine (noradrenaline) and epinephrine (adrenaline) produced by the body, but also many medications like beta blockers, beta2 agonists and alpha2 agonists, which are used to treat high blood pressure and asthma for example.

There are two main groups of adrenoceptors, alpha and beta, with 9 subtypes in total:

alpha types comprise the alpha1 (a Gq coupled receptor) and alpha2 (a Gi coupled receptor)[

alpha1 has 3 subtypes; alpha1A, alpha1B and alpha1D

alpha2 has 3 subtypes; alpha2A, alpha2B and alpha2C

beta types comprise the beta1, beta2 and beta3. All 3 are coupled to Gs proteins, but beta2 and beta3 also couple to Gi

Gi and Gs are linked to adenylyl cyclase. Agonist binding thus causes a rise in the intracellular concentration of the second messenger (Gi inhibits the production of cAMP) cAMP. Downstream effectors of cAMP include cAMP-dependent protein kinase (PKA), which mediates some of the intracellular events following hormone binding.

alpha-Receptors are excitatory mainly to receptors of the eye, gastrointestinal tract and vascular smooth muscle. alpha-Receptors can be further subdivided into two types. alpha-1 Receptors are primarily located in postjunctional positions and initiate postsynaptic excitatory smooth muscle and exocrine gland events. alpha-2 Receptors are primarily presynaptic inhibitors that mediate negative feedback of noradrenaline release and oppose alpha-1 stimulation. alpha-1 Receptors dominate the peripheral nervous system whilst alpha-2 receptors dominate the central nervous system. Central nervous system sympathomimetic effects result from stimulation of central adrenergic neurons. Selective agonists include phenylephrine (alpha-1,2), isoproterenol (beta-1,2), dobutamine (beta-1) and terbutaline (beta-2). Antagonists include phenoxybenzamine, a selective alpha-1 (post-synaptic) blocker and yohimbine, a selective alpha-2 (pre-synaptic) blocker.

CLINICAL EFFECTS OF ADRENORECEPTOR BLOCKAGE and STIMULATION.

alpha	beta-1	beta-2
	STIMULATION	
Mydriasis Vasoconstriction Coronary dilation Decreased GI Motility Bladder contraction	Miosis Tachycardia Increased cardiac contractility Accelerated AV conduction Renin Stimulation	Miosis Vasodilation Bronchodilation Hyperglycaemia Decreased GI motility Bladder relaxation Renin release
	BLOCKADE	
Miosis Postural hypotension Reflex tachycardia Angina (uncommon) Gastric hyperacidity	Hypotension Cardiac arrhythmias Bradycardia Pulmonary oedema Hyperkalaemia (uncommon)	Hypoglycaemia with hypertension Bronchospasm Raynaud's phenomenon Hyperkalaemia (uncommon)

Actions of the alpha2 adrenergic receptor agonists include::

decreased insulin release from the pancreas, increased glucagon release from the pancreas, contraction of sphincters of the GI-tract, negative feedback in the neuronal synapses - presynaptic inhibition of norepinephrine release in CNS, increased platelet aggregation (increased blood clotting tendency), decreases peripheral vascular resistance

alpha2 Agonists can be used to treat: hypertension – decrease blood pressure raising actions of the sympathetic nervous system

alpha2 Antagonists can be used to treat: impotence – relax penile smooth muscles and ease blood flow, depression – enhance mood by increasing norepinephrine secretion.

The alpha2 receptor couples to the Gi/o protein. It is a presynaptic receptor, causing negative feedback on, for example, norepinephrine (NE). When NE is released into the synapse, it feeds back on the alpha2 receptor, causing less NE release from the presynaptic neuron. This decreases the effect of NE. There are also alpha2 receptors on the nerve terminal membrane of the post-synaptic adrenergic neuron.

For clonidine:

Clonidine may potentiate the CNS-depressive effects of alcohol, barbiturates or other sedating drugs.

In patients who have developed localized contact sensitization to clonidine, continuation of treatment or substitution of oral clonidine hydrochloride therapy may be associated with the development of a generalized skin rash.

The sympatholytic action of clonidine may worsen sinus node dysfunction and atrioventricular (AV) block, especially in patients taking other sympatholytic drugs. There are post-marketing reports of patients with conduction abnormalities and/or taking other sympatholytic drugs who developed severe bradycardia requiring IV atropine, IV isoproterenol and temporary cardiac pacing while taking clonidine.

Most adverse effects are mild and tend to diminish with continued therapy. The most frequent (which appear to be dose-related) are dry mouth, occurring in about 40 of 100 patients; drowsiness, about 33 in 100; dizziness, about 16 in 100; constipation and sedation, each about 10 in 100.

Less frequent adverse experiences include

- Body as a Whole: Fatigue, fever, headache, pallor, weakness, and withdrawal syndrome. Also reported were a weakly positive Coombs' test and increased sensitivity to alcohol.
- Cardiovascular: Bradycardia, congestive heart failure, electrocardiographic abnormalities (i.e., sinus node arrest, junctional bradycardia, high degree AV block and arrhythmias), orthostatic symptoms, palpitations, Raynaud's phenomenon, syncope, and tachycardia. Cases of sinus bradycardia and atrioventricular block have been reported, both with and without the use of concomitant digitalis.
- Central Nervous System: Agitation, anxiety, delirium, delusional perception, hallucinations (including visual and auditory), insomnia, mental depression, nervousness, other behavioral changes, paresthesia, restlessness, sleep disorder, and vivid dreams or nightmares.
- Dermatological: Alopecia, angioneurotic edema, hives, pruritus, rash, and urticaria.
- Gastrointestinal: Abdominal pain, anorexia, constipation, hepatitis, malaise, mild transient abnormalities in liver function tests, nausea, parotitis, pseudo-obstruction (including colonic pseudo-obstruction), salivary gland pain, and vomiting.
- Genitourinary: Decreased sexual activity, difficulty in micturition, erectile dysfunction, loss of libido, nocturia, and urinary retention.

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- Hematologic: Thrombocytopenia.
- Metabolic: Gynecomastia, transient elevation of blood glucose or serum creatine phosphokinase, and weight gain.
- Musculoskeletal: Leg cramps and muscle or joint pain.
- Oro-otolaryngeal: Dryness of the nasal mucosa.
- Ophthalmological: Accommodation disorder, blurred vision, burning of the eyes, decreased lacrimation, and dryness of eyes

Carcinogenesis, Mutagenesis, Impairment Of Fertility

Chronic dietary administration of clonidine was not carcinogenic to rats (132 weeks) or mice (78 weeks) dosed, respectively, at up to 46 or 70 times the maximum recommended daily human dose as mg/kg (9 or 6 times the MRDHD on a mg/m² basis).

There was no evidence of genotoxicity in the Ames test for mutagenicity or mouse micronucleus test for clastogenicity.

Fertility of male or female rats was unaffected by clonidine doses as high as 150 µg/kg (approximately 3 times MRDHD). In a separate experiment, fertility of female rats appeared to be affected at dose levels of 500 to 2000 µg/kg (10 to 40 times the oral MRDHD on a mg/kg basis; 2 to 8 times the MRDHD on a mg/m² basis)

Reproduction studies performed in rabbits at doses up to approximately 3 times the oral maximum recommended daily human dose (MRDHD) of clonidine hydrochloride tablets produced no evidence of a teratogenic or embryotoxic potential in rabbits. In rats, however, doses as low as 1/3 the oral MRDHD (1/15 the MRDHD on a mg/m² basis) of clonidine were associated with increased resorptions in a study in which dams were treated continuously from 2 months prior to mating. Increased resorptions were not associated with treatment at the same time or at higher dose levels (up to 3 times the oral MRDHD) when the dams were treated on gestation days 6 to 15. Increases in resorption were observed at much higher dose levels (40 times the oral MRDHD on a mg/kg basis; 4 to 8 time

Class a gpcr modulators adverse effects

Class A G protein-coupled receptors (GPCRs) continue to garner interest for their essential roles in cell signalling and their importance as drug targets. Although numerous drugs in the clinic target these receptors, over 60% GPCRs remain unexploited. Moreover, the adverse effects triggered by the available unbiased GPCR modulators, limit their use and therapeutic value

For G-protein inhibitors:/ antagonists/ modulators.

G protein-coupled receptors (GPCRs) are essential cell membrane signaling molecules and represent the most important class of drug targets. Some signaling pathways downstream of a GPCR may be responsible for drug adverse effects, while others mediate therapeutic efficacy. Biased ligands preferentially activate only a subset of all GPCR signaling pathways. They hold great potential to become next-generation GPCR drugs with less side effects due to their potential to exclusively activate desired signaling pathways.

GPCR ligands include odorants, tastants, and neurotransmitters, and vary in size and properties. Dramatic chemical diversity may occur even among ligands of the same receptor. Chemical variability of antagonists significantly correlates with the binding site hydrophobicity and anti-correlates with the number of hydrogen bond donors in the binding site. The number of disulfide bridges in the extracellular region of a receptor anti-correlates with the range of molecular weights of its antagonists, highlighting the role of the entrance pathway in determining the size selectivity for GPCR antagonists.

The number of protein targets included in the cross-pharmacology profile of the different GPCRs changes significantly upon varying the ligand similarity and binding affinity criteria. However, with the exception of muscarinic receptors, aminergic GPCRs distinguish themselves from the rest of the members in the family by their remarkably high levels of pharmacological similarity among them.

GPCRs are classified under the GRAFS system (Metabotropic Glutamate, Rhodopsin, Adhesion, Frizzled/taste2/Smoothed and Secretin), with therapies having been developed for about 30 GPCRs from the glutamate, rhodopsin and secretin families. GPCR signaling requires significant conformational changes within the trans-membrane TM domain, triggered by agonist binding, and is often coupled to interactions from the extracellular domains or loops. It is becoming clear that many binding sites and mechanisms exist for positive and negative allosteric regulation, and for biased signaling pathways, likely in greater numbers than seen in most other protein systems.

When GPCRs are exposed to a neutral agonist, such as morphine on mu-opioid receptor, an occupied receptor can generate several signal waves (non-biased agonist). In GPCR signaling, the ability of a molecule to selectively activate one pathway without affecting another pathway is called biased agonism. Biased signaling occurs at different signaling proteins, including G proteins, GRKs, beta-arrestins, and even at levels of the allosteric binding site. Since GPCR activation-induced two distinct signal waves, G protein-dependent signaling followed by beta-arrestin-dependent signaling opens a new promising therapeutic future in the world of GPCRs. This is true since discovering such molecules dramatically lowers the adverse effects by turning off unwanted signals. For example, the analgesic effect of morphine (neutral agonist) through the activation of u-receptors is accompanied by several side effects, including constipation, respiratory depression, tolerance, nausea, and sedation

Despite the long history and obvious desirability of developing drugs targeting GPCRs, there are several problems associated with their development. For example, the muscarinic M1 receptor is a well-validated target for agonists that could alleviate cognitive decline during neurodegeneration .

Muscarinic acetylcholine receptors (MRs, or mAChRs), which are more sensitive to muscarine than to nicotine, are a group of class A GPCRs comprising five distinct subtypes, named as muscarinic M1, M2, M3, M4, and M5 receptors (M1R-M5R) M1R, M3R, and M5R are coupled to the Gq/11 family of G proteins, whereas M2R and M4R are coupled to the Gi/o family of G proteins.

However, the orthosteric binding site of M1 is virtually identical to those of the related receptors M2, M3, M4, and M5 as they all bind the native ligand acetylcholine, and activation of M2 and M3 in particular gives rise to dose-limiting side effects (gastrointestinal [GI] disturbances, cardiovascular effects).

Atropine and other anticholinergic agents exert their bronchodilator effects through the blockade of MRs in the airways. As a tertiary ammonium derivative, atropine is a nonselective antagonist with similar affinity for all of the MR subtypes The half-life of atropine for M3R residence is 3.5 hours. Although extensively used in the past, atropine is rarely used at the present time because it is well absorbed into the systemic circulation and penetrates the blood-brain barrier, leading to multiple systemic side effects, including tachycardia.

Several long-acting muscarinic antagonists (LAMAs) are under investigation or are available for the treatment of obstructive airway diseases. LAMAs are considered to be safe drugs at recommended dosages. However, because MRs are expressed not only in the lungs, but also in the heart and the digestive and urinary tracts, the blockade of different MR subtypes in these organs by LAMA treatment can cause diverse, unwanted physiologic effects. For example, these agents can initially block prejunctional M2R on cholinergic airway nerves that normally reduce the release of the bronchoconstricting neurotransmitter acetylcholine, thus resulting in cough and paradoxical bronchoconstriction. Side effects including cardiovascular morbidity and mortality of inhaled LAMA agents in asthma need to be further studied and defined.

Another potential source of side effects when targeting other receptors could arise due to signaling through multiple different pathways

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	<p>There are multiple signaling pathways for GPCRs, and it is sometimes possible to bias the signaling of a given GPCR through either a specific G protein or through beta arrestin which could reduce the side effects of some drugs</p> <p>Targeting G protein alpha-subunits has the potential for pleiotropic effects and could result in multiple side effects. Particular targets of concern include ion channels such as the G protein-activated inward rectifier K⁺ channel (GIRK) and the N-type voltage-gated calcium channels. Gbeta-gamma activates GIRK channels in neurons and in atria, leading to a hyperpolarization-induced decrease in action potential firing. Therefore, when considering the use of Gbeta-gamma inhibitors in cardiac or immune therapy, interfering with the regulation of action potentials would have highly undesirable side effects, such as arrhythmias. However, empirical data using prototypical Gbeta-gamma blockers indicate that these pathways are unaffected by Gbeta-gamma inhibitors, and animals treated with gallein show no signs of arrhythmias or alterations in heart rate.</p>
<p>SODIUM CITRATE</p>	<p>For citric acid (and its inorganic citrate salts)</p> <p>Based on extensive animal testing data and on human experience, citric acid has low acute toxicity. Citric acid is not suspected of causing cancer, birth defects or reproductive toxicity. Further, it does not cause mutations. Also, the sensitizing potential is considered low. In contrast, irritation, particularly of the eyes but also the airways and the skin, is the main hazard presented by citric acid.</p>
<p>BENZYL ALCOHOL</p>	<p>The following information refers to contact allergens as a group and may not be specific to this product.</p> <p>Contact allergies quickly manifest themselves as contact eczema, more rarely as urticaria or Quincke's oedema. The pathogenesis of contact eczema involves a cell-mediated (T lymphocytes) immune reaction of the delayed type. Other allergic skin reactions, e.g. contact urticaria, involve antibody-mediated immune reactions. The significance of the contact allergen is not simply determined by its sensitisation potential: the distribution of the substance and the opportunities for contact with it are equally important. A weakly sensitising substance which is widely distributed can be a more important allergen than one with stronger sensitising potential with which few individuals come into contact. From a clinical point of view, substances are noteworthy if they produce an allergic test reaction in more than 1% of the persons tested.</p> <p>Adverse reactions to fragrances in perfumes and in fragranced cosmetic products include allergic contact dermatitis, irritant contact dermatitis, photosensitivity, immediate contact reactions (contact urticaria), and pigmented contact dermatitis. Airborne and conjugal contact dermatitis occur.</p> <p>Intolerance to perfumes, by inhalation, may occur if the perfume contains a sensitising principal. Symptoms may vary from general illness, coughing, phlegm, wheezing, chest-tightness, headache, exertional dyspnoea, acute respiratory illness, hayfever, and other respiratory diseases (including asthma). Perfumes can induce hyper-reactivity of the respiratory tract without producing an IgE-mediated allergy or demonstrable respiratory obstruction. This was shown by placebo-controlled challenges of nine patients to "perfume mix". The same patients were also subject to perfume provocation, with or without a carbon filter mask, to ascertain whether breathing through a filter with active carbon would prevent symptoms. The patients breathed through the mouth, during the provocations, as a nose clamp was used to prevent nasal inhalation. The patient's earlier symptoms were verified; breathing through the carbon filter had no protective effect. The symptoms were not transmitted via the olfactory nerve but they may have been induced by trigeminal reflex via the respiratory tract or by the eyes.</p> <p>Cases of occupational asthma induced by perfume substances such as isoamyl acetate, limonene, cinnamaldehyde and benzaldehyde, tend to give persistent symptoms even though the exposure is below occupational exposure limits. Inhalation intolerance has also been produced in animals. The emissions of five fragrance products, for one hour, produced various combinations of sensory irritation, pulmonary irritation, decreases in expiratory airflow velocity as well as alterations of the functional observational battery indicative of neurotoxicity in mice. Neurotoxicity was found to be more severe after mice were repeatedly exposed to the fragrance products, being four brands of cologne and one brand of toilet water.</p> <p>Contact allergy to fragrances is relatively common, affecting 1 to 3% of the general population, based on limited testing with eight common fragrance allergens and about 16 % of patients patch tested for suspected allergic contact dermatitis.</p> <p>Contact allergy to fragrance ingredients occurs when an individual has been exposed, on the skin, to a sufficient degree of fragrance contact allergens. Contact allergy is a life-long, specifically altered reactivity in the immune system. This means that once contact allergy is developed, cells in the immune system will be present which can recognise and react towards the allergen. As a consequence, symptoms, i.e. allergic contact dermatitis, may occur upon re-exposure to the fragrance allergen(s) in question. Allergic contact dermatitis is an inflammatory skin disease characterised by erythema, swelling and vesicles in the acute phase. If exposure continues it may develop into a chronic condition with scaling and painful fissures of the skin. Allergic contact dermatitis to fragrance ingredients is most often caused by cosmetic products and usually involves the face and/or hands. It may affect fitness for work and the quality of life of the individual. Fragrance contact allergy has long been recognised as a frequent and potentially disabling problem. Prevention is possible as it is an environmental disease and if the environment is modified (e.g. by reduced use concentrations of allergens), the disease frequency and severity will decrease. Fragrance contact allergy is mostly non-occupational and related to the personal use of cosmetic products. Allergic contact dermatitis can be severe and widespread, with a significant impairment of quality of life and potential consequences for fitness for work. Thus, prevention of contact sensitisation to fragrances, both in terms of primary prevention (avoiding sensitisation) and secondary prevention (avoiding relapses of allergic contact dermatitis in those already sensitised), is an important objective of public health risk management measure.</p> <p>Hands: Contact sensitisation may be the primary cause of hand eczema, or may be a complication of irritant or atopic hand eczema. The number of positive patch tests has been reported to correlate with the duration of hand eczema, indicating that long-standing hand eczema may often be complicated by sensitisation. Fragrance allergy may be a relevant problem in patients with hand eczema; perfumes are present in consumer products to which their hands are exposed. A significant relationship between hand eczema and fragrance contact allergy has been found in some studies based on patients investigated for contact allergy. However, hand eczema is a multi-factorial disease and the clinical significance of fragrance contact allergy in (severe) chronic hand eczema may not be clear.</p> <p>Axillae Bilateral axillary (underarm) dermatitis may be caused by perfume in deodorants and, if the reaction is severe, it may spread down the arms and to other areas of the body. In individuals who consulted a dermatologist, a history of such first-time symptoms was significantly related to the later diagnosis of perfume allergy.</p> <p>Face Facial eczema is an important manifestation of fragrance allergy from the use of cosmetic products (16). In men, after-shave products can cause an eczematous eruption of the beard area and the adjacent part of the neck and men using wet shaving as opposed to dry have been shown to have an increased risk of being fragrance allergic.</p> <p>Irritant reactions (including contact urticaria): Irritant effects of some individual fragrance ingredients, e.g. citral are known. Irritant contact dermatitis from perfumes is believed to be common, but there are no existing investigations to substantiate this. Many more people complain about intolerance or rashes to perfumes/perfumed products than are shown to be allergic by testing. This may be due to irritant effects or inadequate diagnostic procedures. Fragrances may cause a dose-related contact urticaria of the non-immunological type (irritant contact urticaria). Cinnamal, cinnamic alcohol, and Myroxylon pereirae are well recognised causes of contact urticaria, but others, including menthol, vanillin and benzaldehyde have also been reported. The reactions to</p>

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Myroxylon pereirae may be due to cinnamates. A relationship to delayed contact hypersensitivity was suggested, but no significant difference was found between a fragrance-allergic group and a control group in the frequency of immediate reactions to fragrance ingredients in keeping with a nonimmunological basis for the reactions seen.

Pigmentary anomalies: The term "pigmented cosmetic dermatitis" was introduced in 1973 for what had previously been known as melanosia faciei feminae when the mechanism (type IV allergy) and causative allergens were clarified. It refers to increased pigmentation, usually on the face/neck, often following sub-clinical contact dermatitis. Many cosmetic ingredients were patch tested at non-irritant concentrations and statistical evaluation showed that a number of fragrance ingredients were associated: jasmine absolute, ylang-ylang oil, cananga oil, benzyl salicylate, hydroxycitronellal, sandalwood oil, geraniol, geranium oil.

Photo-reactions Musk ambrette produced a considerable number of allergic photocontact reactions (in which UV-light is required) in the 1970s and was later banned from use in the EU. Nowadays, photoallergic contact dermatitis is uncommon. Furocoumarins (psoralens) in some plant-derived fragrance ingredients caused phototoxic reactions with erythema followed by hyperpigmentation resulting in Berloque dermatitis. There are now limits for the amount of furocoumarins in fragrance products. Phototoxic reactions still occur but are rare.

General/respiratory: Fragrances are volatile and therefore, in addition to skin exposure, a perfume also exposes the eyes and naso-respiratory tract. It is estimated that 2-4% of the adult population is affected by respiratory or eye symptoms by such an exposure. It is known that exposure to fragrances may exacerbate pre-existing asthma. Asthma-like symptoms can be provoked by sensory mechanisms. In an epidemiological investigation, a significant association was found between respiratory complaints related to fragrances and contact allergy to fragrance ingredients, in addition to hand eczema, which were independent risk factors in a multivariate analysis.

Fragrance allergens act as haptens, i.e. low molecular weight chemicals that are immunogenic only when attached to a carrier protein. However, not all sensitising fragrance chemicals are directly reactive, but require previous activation. A prohaptens is a chemical that itself is non- or low-sensitising, but that is transformed into a hapten outside the skin by simple chemical transformation (air oxidation, photoactivation) and without the requirement of specific enzymatic systems. A prohaptens is a chemical that itself is non- or low-sensitising but that is transformed into a hapten in the skin (bioactivation) usually via enzyme catalysis. It is not always possible to know whether a particular allergen that is not directly reactive acts as a prohaptens or as a prohaptens, or both, because air oxidation and bioactivation can often give the same product (geraniol is an example). Some chemicals might act by all three pathways.

Prohaptens

Compounds that are bioactivated in the skin and thereby form haptens are referred to as prohaptens.

In the case of prohaptens, the possibility to become activated is inherent to the molecule and activation cannot be avoided by extrinsic measures. Activation processes increase the risk for cross-reactivity between fragrance substances. Crossreactivity has been shown for certain alcohols and their corresponding aldehydes, i.e. between geraniol and geranial (citral) and between cinnamyl alcohol and cinnamal.

The human skin expresses enzyme systems that are able to metabolise xenobiotics, modifying their chemical structure to increase hydrophilicity and allow elimination from the body. Xenobiotic metabolism can be divided into two phases: phase I and phase II. Phase I transformations are known as activation or functionalisation reactions, which normally introduce or unmask hydrophilic functional groups. If the metabolites are sufficiently polar at this point they will be eliminated. However, many phase I products have to undergo subsequent phase II transformations, i.e. conjugation to make them sufficiently water soluble to be eliminated. Although the purpose of xenobiotic metabolism is detoxification, it can also convert relatively harmless compounds into reactive species. Cutaneous enzymes that catalyse phase I transformations include the cytochrome P450 mixed-function oxidase system, alcohol and aldehyde dehydrogenases, monoamine oxidases, flavin-containing monooxygenases and hydrolytic enzymes. Acyltransferases, glutathione S-transferases, UDP-glucuronosyltransferases and sulfotransferases are examples of phase II enzymes that have been shown to be present in human skin. These enzymes are known to catalyse both activating and deactivating biotransformations, but the influence of the reactions on the allergenic activity of skin sensitisers has not been studied in detail. Skin sensitising prohaptens can be recognised and grouped into chemical classes based on knowledge of xenobiotic bioactivation reactions, clinical observations and/or in vivo and in vitro studies of sensitisation potential and chemical reactivity.

QSAR prediction: The relationships between molecular structure and reactivity that form the basis for structural alerts are based on well established principles of mechanistic organic chemistry. Examples of structural alerts are aliphatic aldehydes (alerting to the possibility of sensitisation via a Schiff base reaction with protein amino groups), and alpha,beta-unsaturated carbonyl groups, C=C-CO- (alerting to the possibility of sensitisation via Michael addition of protein thiol groups). Prediction of the sensitisation potential of compounds that can act via abiotic or metabolic activation (pre- or prohaptens) is more complex compared to that of compounds that act as direct haptens without any activation. The autoxidation patterns can differ due to differences in the stability of the intermediates formed, e.g. it has been shown that autoxidation of the structural isomers linalool and geraniol results in different major haptens/allergens. Moreover, the complexity of the prediction increases further for those compounds that can act both as pre- and prohaptens. In such cases, the impact on the sensitisation potency depends on the degree of abiotic activation (e.g. autoxidation) in relation to the metabolic activation

CYP1A2 is a member of the cytochrome P450 super family, is one of the best characterized. It is responsible for the metabolism of commonly drugs belonging to classes such as antidepressants, antipsychotics, mood stabilizers, beta blockers and sedative/hypnotics CYP1A2 also metabolises a number of procarcinogens (such as those in cigarettes). Cigarette smoking may lead to three fold increase in 1A2 activity, which explains why smokers require higher doses of beta blockers than non-smokers

Drugs that inhibit CYP1A2 will predictably increase the plasma concentrations of the medications or decrease in clearance of substrates. Drugs such as ciprofloxacin, fluvoxamine, verapamil, cimetidine, caffeine and isoniazid are inhibitors of CYP1A2 enzyme. Vegetables such as grape fruit juice, cumic and turmeric are inhibitors of the CYP1A2 enzyme which may lead to increase plasma concentration of psychotropics

Inhibition of NF- κ B in vivo can be detrimental. NF- κ B controls multiple functions in homeostasis including a functional immune response, cell cycle, and cell death. Genetic studies in mice and analysis of naturally occurring mutations in humans point to specific developmental and immune consequences due to altering NF- κ B activity.

The same functions that make NF- κ B attractive for developing inhibitors for treating disease also play a role in homeostasis, and disruption of the NF- κ B pathway during development or in adults leads to unfavorable and potentially unhealthy consequences. NF- κ B plays a role in multiple homeostatic cellular processes including response to stimuli, cell proliferation, and death, regulating communication between cells, but is also tightly linked with other signaling pathways within the cell, such as p38 and JNK. In addition to mediating proinflammatory responses, NF- κ B may regulate apoptotic and cell cycle changes induced by cellular stress, DNA damage or oncogenes by communication with the tumor suppressor p53. Disruption of normal cellular responses by inhibiting NF- κ B can have adverse consequences such as immune suppression and tissue damage.

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Understanding the consequences of lack of NF- κ B activity in adult humans comes from observation of naturally occurring genetic deficiencies in this pathway. Mutations have been discovered in humans in signaling molecules upstream of NF- κ B resulting in defects in development or immunity. Genetic defects have also been discovered in genes that immediately affect NF- κ B activation including IKK gamma (NEMO), a subunit of the IKK complex, and I κ Balpha. The IKK gamma mutations result in a defective IKK complex and the I κ Balpha mutation results in an I κ Balpha protein that cannot be phosphorylated and degraded. Both genetic defects result in suppressed NF- κ B activation and ectodermal dysplasia with immunodeficiency. In general patients with these genetic defects have multiple immunological defects including impaired innate immunity, impaired antibody production, and ultimately severe bacterial infections. Understanding the immune defects and susceptibilities in patients with genetic defects in the NF- κ B pathway will help prepare for potential adverse effects of pharmacologic NF- κ B inhibitors.

The requirement for NF- κ B in the development and maintenance of the immune system is well documented. NF- κ B is required for survival during fetal development and for normal lymphocyte generation in adult mice. Removal of the p65 (RelA) subunit of NF- κ B or the IKKbeta gene results in death during fetal development primarily due to massive liver apoptosis. Fetal liver stem cells from p65 or IKKbeta deficient mice have been transplanted into irradiated hosts revealing a specific requirement of NF- κ B for T-cells, B-cells, and common lymphoid progenitor development but not for myeloid cells or stem cells. The failure to produce lymphocytes is mediated through hypersensitivity to TNF due to lack of NF- κ B activity. Lymphocyte depletion with chemical or genetic inhibition of NF- κ B have implications for therapeutic potential use in humans. The double-sided nature of NF- κ B inhibition is clear in this instance where chemical inhibition in vivo mimics genetic experiments inducing rapid TNF-dependent apoptosis. Rapid induction of apoptosis may be an advantage for treating some forms of cancer, but at the same time cause depletion of some lymphocyte populations.

In addition to controlling lymphocyte development, NF- κ B plays a major role in both adaptive and innate immunity. Various signaling pathways responding to receptor recognition of immune challenge converge on NF- κ B which then regulates genes that control the immune response. Both T-cell receptor and B-cell receptors activate NF- κ B through phosphorylation of CARMA1 by PKC theta and PKC beta respectively, resulting in recruitment and activation of IKK and ultimately expression of genes that control cellular activation, proliferation, and survival. In addition, NF- κ B plays a role in T-cell response to costimulatory signals. Cells respond to pathogenic microorganisms in part through recognition by Toll-like receptors (TLRs). TLR-family members recognize different molecular structures present in microbes and respond by activating signaling pathways including NF- κ B leading to expression of anti-microbial effector molecules, as well as molecules that help in development of the adaptive immune response. Inhibition of NF- κ B during TLR stimulation can lead to macrophage apoptosis, a mechanism used by some pathogens to help evade immune response. NF- κ B is clearly required for normal mature B-cell and T-cell maintenance and function, including regulatory, memory, and natural killer-like T cells. Inhibition of NF- κ B activation in lymphocytes results in defects in growth, survival, and cytokine production and blocks multiple steps in germinal center formation. Given the diverse roles NF- κ B plays in immune response to pathogens it is not surprising to find mice genetically deficient in components of the NF- κ B pathway are susceptible to parasitic and bacterial infection.

The role of NF- κ B in inhibition of apoptosis is one of the factors that make it a potential target for cancer therapy. NF- κ B deficient mice die during embryogenesis in part due to TNF-mediated liver damage. Adult mice with impaired NF- κ B targeted to the liver have normal liver function, but have severe liver damage after challenge with concanavalin A, a pan-T cell activator. Liver damage occurs due to sustained activation of JNK due to accumulation of reactive oxygen species (ROS) in the absence of normal NF- κ B activation.

The aryl alkyl alcohol (AAA) fragrance ingredients are a diverse group of chemical structures with similar metabolic and toxicity profiles.

The AAA fragrances demonstrate low acute and subchronic dermal and oral toxicity.

At concentrations likely to be encountered by consumers, AAA fragrance ingredients are non-irritating to the skin.

The potential for eye irritation is minimal.

With the exception of benzyl alcohol and to a lesser extent phenethyl and 2-phenoxyethyl AAA alcohols, human sensitization studies, diagnostic patch tests and human induction studies, indicate that AAA fragrance ingredients generally have no or low sensitization potential. Available data indicate that the potential for photosensitization is low.

NOAELs for maternal and developmental toxicity are far in excess of current human exposure levels.

No carcinogenicity in rats or mice was observed in 2-year chronic testing of benzyl alcohol or a-methylbenzyl alcohol; the latter did induce species and gender-specific renal adenomas in male rats at the high dose. There was no to little genotoxicity, mutagenicity, or clastogenicity in the mutagenicity in vitro bacterial assays, and in vitro mammalian cell assays. All in vivo micronucleus assays were negative.

It is concluded that these materials would not present a safety concern at current levels of use as fragrance ingredients. The Research Institute for Fragrance Materials (RIFM) Expert Panel

A member or analogue of a group of benzyl derivatives generally regarded as safe (GRAS) based in part on their self-limiting properties as flavouring substances in food; their rapid absorption, metabolic detoxification, and excretion in humans and other animals, their low level of flavour use, the wide margin of safety between the conservative estimates of intake and the no-observed-adverse effect levels determined from chronic and subchronic studies and the lack of significant genotoxic and mutagenic potential. This evidence of safety is supported by the fact that the intake of benzyl derivatives as natural components of traditional foods is greater than the intake as intentionally added flavouring substances.

All members of this group are aromatic primary alcohols, aldehydes, carboxylic acids or their corresponding esters or acetals.

The substances in this group:

- contain a benzene ring substituted with a reactive primary oxygenated functional group or can be hydrolysed to such a functional group
- the major pathway of metabolic detoxification involves hydrolysis and oxidation to yield the corresponding benzoic acid derivative which is excreted either as the free acid or the glycine conjugate
- they show a consistent pattern of toxicity in both short- and long- term studies and
- they exhibit no evidence of genotoxicity in standardised batteries of in vitro and in vivo assays.

The benzyl derivatives are rapidly absorbed through the gut, metabolised primarily in the liver, and excreted in the urine as glycine conjugates of benzoic acid derivatives.

In general, aromatic esters are hydrolysed in vivo through the catalytic activity of carboxylesterases, the most important of which are the A-esterases. Hydrolysis of benzyl and benzoate esters to yield corresponding alcohols and carboxylic acids and hydrolysis of acetals to yield benzaldehyde and simple alcohols have been reported in several experiments.

The alcohols and aldehydes are rapidly oxidised to benzoic acid while benzoate esters are hydrolysed to benzoic acid.

Flavor and Extract Manufacturers Association (FEMA)

The material may cause skin irritation after prolonged or repeated exposure and may produce on contact skin redness, swelling, the production of vesicles, scaling and thickening of the skin.

For benzyl alkyl alcohols:

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Unlike benzylic alcohols, the beta-hydroxyl group of the members of this cluster is unlikely to undergo phase II metabolic activation. Instead, the beta-hydroxyl group is expected to contribute to detoxification via oxidation to hydrophilic acid. Despite structural similarity to carcinogenic ethyl benzene, only a marginal concern has been assigned to phenethyl alcohol due to limited mechanistic analogy.

For benzoates:

Acute toxicity: Benzyl alcohol, benzoic acid and its sodium and potassium salt can be considered as a single category regarding human health, as they are all rapidly metabolised and excreted via a common pathway within 24 hrs. Systemic toxic effects of similar nature (e.g. liver, kidney) were observed. However with benzoic acid and its salts toxic effects are seen at higher doses than with benzyl alcohol.

The compounds exhibit low acute toxicity as for the oral and dermal route. The LD50 values are > 2000 mg/kg bw except for benzyl alcohol which needs to be considered as harmful by the oral route in view of an oral LD50 of 1610 mg/kg bw. The 4 hrs inhalation exposure of benzyl alcohol or benzoic acid at 4 and 12 mg/l as aerosol/dust respectively gave no mortality, showing low acute toxicity by inhalation for these compounds.

Benzoic acid and benzyl alcohol are slightly irritating to the skin, while sodium benzoate was not skin irritating. No data are available for potassium benzoate but it is also expected not to be skin irritating. Benzoic acid and benzyl alcohol are irritating to the eye and sodium benzoate was only slightly irritating to the eye. No data are available for potassium benzoate but it is expected also to be only slightly irritating to the eye.

Sensitisation: The available studies for benzoic acid gave no indication for a sensitising effect in animals, however occasionally very low positive reactions were recorded with humans (dermatological patients) in patch tests. The same occurs for sodium benzoate. It has been suggested that the very low positive reactions are non-immunologic contact urticaria. Benzyl alcohol gave positive and negative results in animals. Benzyl alcohol also demonstrated a maximum incidence of sensitization of only 1% in human patch testing. Over several decades no sensitization with these compounds has been seen among workers.

Repeat dose toxicity: For benzoic acid repeated dose oral toxicity studies give a NOAEL of 800 mg/kg/day. For the salts values > 1000 mg/kg/day are obtained. At higher doses increased mortality, reduced weight gain, liver and kidney effects were observed.

For benzyl alcohol the long-term studies indicate a NOAEL > 400 mg/kg bw/d for rats and > 200 mg/kg bw/d for mice. At higher doses effects on bodyweights, lesions in the brains, thymus, skeletal muscle and kidney were observed. It should be taken into account that administration in these studies was by gavage route, at which saturation of metabolic pathways is likely to occur.

Mutagenicity: All chemicals showed no mutagenic activity in *in vitro* Ames tests. Various results were obtained with other *in vitro* genotoxicity assays. Sodium benzoate and benzyl alcohol showed no genotoxicity *in vivo*. While some mixed and/or equivocal *in vitro* chromosomal/chromatid responses have been observed, no genotoxicity was observed in the *in vivo* cytogenetic, micronucleus, or other assays. The weight of the evidence of the *in vitro* and *in vivo* genotoxicity data indicates that these chemicals are not mutagenic or clastogenic. They also are not carcinogenic in long-term carcinogenicity studies.

In a 4-generation study with benzoic acid no effects on reproduction were seen (NOAEL: 750 mg/kg). No compound related effects on reproductive organs (gross and histopathology examination) could be found in the (sub) chronic studies in rats and mice with benzyl acetate, benzyl alcohol, benzaldehyde, sodium benzoate and supports a non-reprotoxic potential of these compounds. In addition, data from reprotoxicity studies on benzyl acetate (NOAEL >2000 mg/kg bw/d; rats and mice) and benzaldehyde (tested only up to 5 mg/kg bw; rats) support the non-reprotoxicity of benzyl alcohol and benzoic acid and its salts.

Developmental toxicity: In rats for sodium benzoate dosed via food during the entire gestation developmental effects occurred only in the presence of marked maternal toxicity (reduced food intake and decreased body weight) (NOAEL = 1400 mg/kg bw). For hamster (NOEL: 300 mg/kg bw), rabbit (NOEL: 250 mg/kg bw) and mice (CD-1 mice, NOEL: 175 mg/kg bw) no higher doses (all by gavage) were tested and no maternal toxicity was observed. For benzyl alcohol: NOAEL= 550 mg/kg bw (gavage; CD-1 mice). LOAEL = 750 mg/kg bw (gavage mice). In this study maternal toxicity was observed e.g. increased mortality, reduced body weight and clinical toxicology. Benzyl acetate: NOEL = 500 mg/kg bw (gavage rats). No maternal toxicity was observed.

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 either not available or does not fill the criteria for classification
 ✓ – Data available to make classification

SECTION 12 Ecological information

Toxicity

Ilium Xylazil-100 Analgesic, Sedative and Muscle Relaxant Injection	Endpoint	Test Duration (hr)	Species	Value	Source
	Not Available	Not Available	Not Available	Not Available	Not Available
xylazine hydrochloride	Endpoint	Test Duration (hr)	Species	Value	Source
	Not Available	Not Available	Not Available	Not Available	Not Available
sodium citrate	Endpoint	Test Duration (hr)	Species	Value	Source
	EC50	48h	Crustacea	>50mg/l	2
	EC50	96h	Algae or other aquatic plants	>18000-32000mg/l	1

Continued...

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	EC50(ECx)	48h	Crustacea	>50mg/l	2
benzyl alcohol	Endpoint	Test Duration (hr)	Species	Value	Source
	EC50	48h	Crustacea	230mg/l	2
	EC50	72h	Algae or other aquatic plants	500mg/l	2
	NOEC(ECx)	336h	Fish	5.1mg/l	2
	EC50	96h	Algae or other aquatic plants	76.828mg/l	2
	LC50	96h	Fish	10mg/l	2

Legend: Extracted from 1. IUCLID Toxicity Data 2. Europe ECHA Registered Substances - Ecotoxicological Information - Aquatic Toxicity 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

DO NOT discharge into sewer or waterways.

Persistence and degradability

Ingredient	Persistence: Water/Soil	Persistence: Air
xylazine hydrochloride	HIGH	HIGH
benzyl alcohol	LOW	LOW

Bioaccumulative potential

Ingredient	Bioaccumulation
xylazine hydrochloride	HIGH (LogKOW = 4.52)
sodium citrate	LOW (LogKOW = -0.28)
benzyl alcohol	LOW (LogKOW = 1.1)

Mobility in soil

Ingredient	Mobility
xylazine hydrochloride	LOW (Log KOC = 3875)
benzyl alcohol	LOW (Log KOC = 15.66)

SECTION 13 Disposal considerations

Waste treatment methods

Product / Packaging disposal	<ul style="list-style-type: none"> ▶ Containers may still present a chemical hazard/ danger when empty. ▶ Return to supplier for reuse/ recycling if possible.
	<p>Otherwise:</p> <ul style="list-style-type: none"> ▶ If container can not be cleaned sufficiently well to ensure that residuals do not remain or if the container cannot be used to store the same product, then puncture containers, to prevent re-use, and bury at an authorised landfill. ▶ Where possible retain label warnings and SDS and observe all notices pertaining to the product. ▶ DO NOT allow wash water from cleaning or process equipment to enter drains. ▶ It may be necessary to collect all wash water for treatment before disposal. ▶ In all cases disposal to sewer may be subject to local laws and regulations and these should be considered first. ▶ Where in doubt contact the responsible authority. ▶ Recycle wherever possible. ▶ Consult manufacturer for recycling options or consult local or regional waste management authority for disposal if no suitable treatment or disposal facility can be identified. ▶ Dispose of by: burial in a land-fill specifically licensed to accept chemical and / or pharmaceutical wastes or incineration in a licensed apparatus (after admixture with suitable combustible material). ▶ Decontaminate empty containers. Observe all label safeguards until containers are cleaned and destroyed.

SECTION 14 Transport information

Labels Required

Marine Pollutant	NO
HAZCHEM	Not Applicable

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

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

Continued...

Sea transport (IMDG-Code / GGVSee): NOT REGULATED FOR TRANSPORT OF DANGEROUS GOODS**14.7. Maritime transport in bulk according to IMO instruments****14.7.1. Transport in bulk according to Annex II of MARPOL and the IBC code**

Not Applicable

14.7.2. Transport in bulk in accordance with MARPOL Annex V and the IMSBC Code

Product name	Group
xylazine hydrochloride	Not Available
sodium citrate	Not Available
benzyl alcohol	Not Available

14.7.3. Transport in bulk in accordance with the IGC Code

Product name	Ship Type
xylazine hydrochloride	Not Available
sodium citrate	Not Available
benzyl alcohol	Not Available

SECTION 15 Regulatory information**Safety, health and environmental regulations / legislation specific for the substance or mixture****xylazine hydrochloride is found on the following regulatory lists**

Australia Chemicals with non-industrial uses removed from the Australian Inventory of Chemical Substances (old Inventory)

Australia Standard for the Uniform Scheduling of Medicines and Poisons (SUSMP) - Schedule 4

FEI Equine Prohibited Substances List - Controlled Medication

FEI Equine Prohibited Substances List (EPSL)

sodium citrate is found on the following regulatory lists

Australian Inventory of Industrial Chemicals (AIIC)

benzyl alcohol is found on the following regulatory lists

Australia Hazardous Chemical Information System (HCIS) - Hazardous Chemicals

Australian Inventory of Industrial Chemicals (AIIC)

Additional Regulatory Information

Not Applicable

National Inventory Status

National Inventory	Status
Australia - AIIC / Australia Non-Industrial Use	Yes
Canada - DSL	No (xylazine hydrochloride)
Canada - NDSL	No (xylazine hydrochloride; benzyl alcohol)
China - IECSC	No (xylazine hydrochloride)
Europe - EINEC / ELINCS / NLP	Yes
Japan - ENCS	No (xylazine hydrochloride)
Korea - KECI	No (xylazine hydrochloride)
New Zealand - NZIoC	Yes
Philippines - PICCS	No (xylazine hydrochloride)
USA - TSCA	TSCA Inventory 'Active' substance(s) (sodium citrate; benzyl alcohol); No (xylazine hydrochloride)
Taiwan - TCSI	Yes
Mexico - INSQ	No (xylazine hydrochloride)
Vietnam - NCI	Yes
Russia - FBEPH	No (xylazine hydrochloride)
Legend:	Yes = All CAS declared ingredients are on the inventory No = One or more of the CAS listed ingredients are not on the inventory. These ingredients may be exempt or will require registration.

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SECTION 16 Other information

Revision Date	10/03/2023
Initial Date	04/05/2020

SDS Version Summary

Version	Date of Update	Sections Updated
4.1	23/12/2022	Classification review due to GHS Revision change.
5.1	10/03/2023	Classification change due to full database hazard calculation/update.

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.

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
- ▶ ES: Exposure Standard
- ▶ 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
- ▶ DNEL: Derived No-Effect Level
- ▶ PNEC: Predicted no-effect concentration
- ▶ MARPOL: International Convention for the Prevention of Pollution from Ships
- ▶ IMSBC: International Maritime Solid Bulk Cargoes Code
- ▶ IGC: International Gas Carrier Code
- ▶ IBC: International Bulk Chemical Code

- ▶ AIIC: Australian Inventory of Industrial Chemicals
- ▶ DSL: Domestic Substances List
- ▶ NDSL: Non-Domestic Substances List
- ▶ IECSC: Inventory of Existing Chemical Substance in China
- ▶ EINECS: European INventory of Existing Commercial chemical Substances
- ▶ ELINCS: European List of Notified Chemical Substances
- ▶ NLP: No-Longer Polymers
- ▶ ENCS: Existing and New Chemical Substances Inventory
- ▶ KECI: Korea Existing Chemicals Inventory
- ▶ NZIoC: New Zealand Inventory of Chemicals
- ▶ PICCS: Philippine Inventory of Chemicals and Chemical Substances
- ▶ TSCA: Toxic Substances Control Act
- ▶ TCSI: Taiwan Chemical Substance Inventory
- ▶ INSQ: Inventario Nacional de Sustancias Químicas
- ▶ NCI: National Chemical Inventory
- ▶ FBEPH: Russian Register of Potentially Hazardous Chemical and Biological Substances

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TEL (+61 3) 9572 4700.