

# Virbac SEBAZOLE Keratolytic, Keratoplastic, Antibacterial, Antifungal & Antipruritic Wash for Dogs & Cats

Virbac (Australia) Pty Limited

Chemwatch Hazard Alert Code: 3

Chemwatch: 24-8816

Issue Date: 01/19/2017

Version No: 3.1.1.1

Print Date: 01/23/2017

Safety Data Sheet according to WHS and ADG requirements

L.GHS.AUS.EN

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

### Product Identifier

<b>Product name</b>	Virbac SEBAZOLE Keratolytic, Keratoplastic, Antibacterial, Antifungal & Antipruritic Wash for Dogs & Cats
<b>Synonyms</b>	APVMA No: 47648
<b>Other means of identification</b>	Not Available

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

<b>Relevant identified uses</b>	Topical shampoo for dogs and cats.
---------------------------------	------------------------------------

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

<b>Registered company name</b>	Virbac (Australia) Pty Limited
<b>Address</b>	361 Horsley Road Milperra NSW 2214 Australia
<b>Telephone</b>	1800 242 100
<b>Fax</b>	+61 2 9772 9773
<b>Website</b>	www.virbac.com.au
<b>Email</b>	au_customerservice@virbac.com.au

### Emergency telephone number

<b>Association / Organisation</b>	Poisons Information Centre
<b>Emergency telephone numbers</b>	13 11 26
<b>Other emergency telephone numbers</b>	Not Available

## SECTION 2 HAZARDS IDENTIFICATION

### Classification of the substance or mixture

<b>Poisons Schedule</b>	S6
<b>Classification</b> <sup>[1]</sup>	Acute Toxicity (Oral) Category 4, Skin Corrosion/Irritation Category 2, Serious Eye Damage Category 1, Specific target organ toxicity - single exposure Category 3 (respiratory tract irritation), Acute Aquatic Hazard Category 3, Chronic Aquatic Hazard Category 3
<b>Legend:</b>	1. Classified by Chemwatch; 2. Classification drawn from HSIS ; 3. Classification drawn from EC Directive 1272/2008 - Annex VI

### Label elements

<b>GHS label elements</b>	
---------------------------	---

## Virbac SEBAZOLE Keratolytic, Keratoplastic, Antibacterial, Antifungal & Antipruritic Wash for Dogs & Cats

SIGNAL WORD	<b>DANGER</b>
-------------	---------------

### Hazard statement(s)

<b>H302</b>	Harmful if swallowed.
<b>H315</b>	Causes skin irritation.
<b>H318</b>	Causes serious eye damage.
<b>H335</b>	May cause respiratory irritation.
<b>H412</b>	Harmful to aquatic life with long lasting effects.

### Precautionary statement(s) Prevention

<b>P271</b>	Use only outdoors or in a well-ventilated area.
<b>P280</b>	Wear protective gloves/protective clothing/eye protection/face protection.
<b>P261</b>	Avoid breathing mist/vapours/spray.
<b>P270</b>	Do not eat, drink or smoke when using this product.
<b>P273</b>	Avoid release to the environment.

### Precautionary statement(s) Response

<b>P305+P351+P338</b>	IF IN EYES: Rinse cautiously with water for several minutes. Remove contact lenses, if present and easy to do. Continue rinsing.
<b>P310</b>	Immediately call a POISON CENTER or doctor/physician.
<b>P362</b>	Take off contaminated clothing and wash before reuse.
<b>P301+P312</b>	IF SWALLOWED: Call a POISON CENTER or doctor/physician if you feel unwell.
<b>P302+P352</b>	IF ON SKIN: Wash with plenty of soap and water.
<b>P304+P340</b>	IF INHALED: Remove victim to fresh air and keep at rest in a position comfortable for breathing.
<b>P330</b>	Rinse mouth.
<b>P332+P313</b>	If skin irritation occurs: Get medical advice/attention.

### Precautionary statement(s) Storage

<b>P405</b>	Store locked up.
<b>P403+P233</b>	Store in a well-ventilated place. Keep container tightly closed.

### Precautionary statement(s) Disposal

<b>P501</b>	Dispose of contents/container in accordance with local regulations.
-------------	---

## SECTION 3 COMPOSITION / INFORMATION ON INGREDIENTS

### Substances

See section below for composition of Mixtures

### Mixtures

CAS No	%[weight]	Name
7772-98-7	1-10	<u>sodium thiosulfate</u> (75g/L)
54-21-7	1-5	<u>sodium salicylate</u> (35g/L)
88-04-0	0-1	<u>4-chloro-3,5-xyleneol</u> (5.4g/L)
24169-02-6	0-1	<u>econazole nitrate</u> (10g/L)
151-21-3	10-20	<u>sodium lauryl sulfate</u>
68603-42-9	1-10	<u>coconut diethanolamide</u>
41593-38-8	1-2	<u>propylene glycol phenyl ether</u>
Not Available	>60	Ingredients determined not to be hazardous

Continued...

## Virbac SEBAZOLE Keratolytic, Keratoplastic, Antibacterial, Antifungal & Antipruritic Wash for Dogs & Cats

### SECTION 4 FIRST AID MEASURES

#### Description of first aid measures

<b>Eye Contact</b>	<p>If this product comes in contact with the eyes:</p> <ul style="list-style-type: none"> <li>▶ Immediately hold eyelids apart and flush the eye continuously with running water.</li> <li>▶ Ensure complete irrigation of the eye by keeping eyelids apart and away from eye and moving the eyelids by occasionally lifting the upper and lower lids.</li> <li>▶ Continue flushing until advised to stop by the Poisons Information Centre or a doctor, or for at least 15 minutes.</li> <li>▶ Transport to hospital or doctor without delay.</li> <li>▶ Removal of contact lenses after an eye injury should only be undertaken by skilled personnel.</li> </ul>
<b>Skin Contact</b>	<p>If skin contact occurs:</p> <ul style="list-style-type: none"> <li>▶ Immediately remove all contaminated clothing, including footwear.</li> <li>▶ Flush skin and hair with running water (and soap if available).</li> <li>▶ Seek medical attention in event of irritation.</li> </ul>
<b>Inhalation</b>	<ul style="list-style-type: none"> <li>▶ If fumes or combustion products are inhaled remove from contaminated area.</li> <li>▶ Lay patient down. Keep warm and rested.</li> <li>▶ Prostheses such as false teeth, which may block airway, should be removed, where possible, prior to initiating first aid procedures.</li> <li>▶ Apply artificial respiration if not breathing, preferably with a demand valve resuscitator, bag-valve mask device, or pocket mask as trained. Perform CPR if necessary.</li> <li>▶ Transport to hospital, or doctor, without delay.</li> </ul>
<b>Ingestion</b>	<ul style="list-style-type: none"> <li>▶ <b>IF SWALLOWED, REFER FOR MEDICAL ATTENTION, WHERE POSSIBLE, WITHOUT DELAY.</b></li> <li>▶ For advice, contact a Poisons Information Centre or a doctor.</li> <li>▶ Urgent hospital treatment is likely to be needed.</li> <li>▶ In the mean time, qualified first-aid personnel should treat the patient following observation and employing supportive measures as indicated by the patient's condition.</li> <li>▶ If the services of a medical officer or medical doctor are readily available, the patient should be placed in his/her care and a copy of the SDS should be provided. Further action will be the responsibility of the medical specialist.</li> <li>▶ If medical attention is not available on the worksite or surroundings send the patient to a hospital together with a copy of the SDS.</li> </ul> <p><b>Where medical attention is not immediately available or where the patient is more than 15 minutes from a hospital or unless instructed otherwise:</b></p> <ul style="list-style-type: none"> <li>▶ <b>INDUCE</b> vomiting with fingers down the back of the throat, <b>ONLY IF CONSCIOUS</b>. Lean patient forward or place on left side (head-down position, if possible) to maintain open airway and prevent aspiration.</li> </ul> <p><b>NOTE:</b> Wear a protective glove when inducing vomiting by mechanical means.</p>

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

for salicylate intoxication:

- ▶ Pending gastric lavage, use emetics such as syrup of Ipecac or delay gastric emptying and absorption by swallowing a slurry of activated charcoal. **Do not give ipecac after charcoal.**
- ▶ Gastric lavage with water or perhaps sodium bicarbonate solution (3%-5%). Mild alkali delays salicylate absorption from the stomach and perhaps slightly from the duodenum.
- ▶ Saline catharsis with sodium or magnesium sulfate (15-30 gm in water).
- ▶ Take an immediate blood sample for an appraisal of the patient's acid-base status. A pH determination on an anaerobic sample of arterial blood is best. An analysis of the plasma salicylate concentration should be made at the same time. Laboratory controls are almost essential for the proper management of severe salicylism.
- ▶ In the presence of an established acidosis, alkali therapy is essential, but at least in an adult, alkali should be withheld until its need is demonstrated by chemical analysis. The intensity of treatment depends on the intensity of acidosis. In the presence of vomiting, intravenous sodium bicarbonate is the most satisfactory of all alkali therapy.
- ▶ Correct dehydration and hypoglycaemia (if present) by the intravenous administration of glucose in water or in isotonic saline. The administration of glucose may also serve to remedy ketosis which is often seen in poisoned children.
- ▶ Even in patients without hypoglycaemia, infusions of glucose adequate to produce distinct hyperglycaemia are recommended to prevent glucose depletion in the brain. This recommendation is based on impressive experimental data in animals.
- ▶ Renal function should be supported by correcting dehydration and incipient shock. Overhydration is not justified. An alkaline urine should be maintained by the administration of alkali if necessary with care to prevent a severe systemic alkalosis. As long as urine remains alkaline (pH above 7.5), administration of an osmotic diuretic such as mannitol or perhaps THAM is useful, but one must be careful to avoid hypokalaemia. Supplements of potassium chloride should be included in parenteral fluids.
- ▶ Small doses of barbiturates, diazepam, paraldehyde, or perhaps other sedatives (but probably not morphine) may be required to suppress extreme restlessness and convulsions.
- ▶ For hyperpyrexia, use sponge baths.

The presence of petechiae or other signs of haemorrhagic tendency calls for a large Vitamin K dose and perhaps ascorbic acid. Minor transfusions may be necessary since bleeding in salicylism is not always due to a prothrombin effect.

## Virbac SEBAZOLE Keratolytic, Keratoplastic, Antibacterial, Antifungal & Antipruritic Wash for Dogs & Cats

- ▶ Haemodialysis and haemoperfusion have proved useful in salicylate poisoning, as have peritoneal dialysis and exchange transfusions, but alkaline diuretic therapy is probably sufficient except in fulminating cases.

[GOSSELIN, et.al.: *Clinical Toxicology of Commercial Products*]

The mechanism of the toxic effect involves metabolic acidosis, respiratory alkalosis, hypoglycaemia, and potassium depletion. Salicylate poisoning is characterised by extreme acid-base disturbances, electrolyte disturbances and decreased levels of consciousness. There are differences between acute and chronic toxicity and a varying clinical picture which is dependent on the age of the patient and their kidney function. The major feature of poisoning is metabolic acidosis due to "uncoupling of oxidative phosphorylation" which produces an increased metabolic rate, increased oxygen consumption, increased formation of carbon dioxide, increased heat production and increased utilisation of glucose. Direct stimulation of the respiratory centre leads to hyperventilation and respiratory alkalosis. This leads to compensatory increased renal excretion of bicarbonate which contributes to the metabolic acidosis which may coexist or develop subsequently. Hypoglycaemia may occur as a result of increased glucose demand, increased rates of tissue glycolysis, and impaired rate of glucose synthesis. **NOTE:** Tissue glucose levels may be lower than plasma levels. Hyperglycaemia may occur due to increased glycogenolysis. Potassium depletion occurs as a result of increased renal excretion as well as intracellular movement of potassium.

Salicylates competitively inhibit vitamin K dependent synthesis of factors II, VII, IX, X and in addition, may produce a mild dose dependent hepatitis. Salicylates are bound to albumin. The extent of protein binding is concentration dependent (and falls with higher blood levels). This, and the effects of acidosis, decreasing ionisation, means that the volume of distribution increases markedly in overdose as does CNS penetration. The extent of protein binding (50-80%) and the rate of metabolism are concentration dependent. Hepatic clearance has zero order kinetics and thus the therapeutic half-life of 2-4.5 hours but the half-life in overdose is 18-36 hours. Renal excretion is the most important route in overdose. Thus when the salicylate concentrations are in the toxic range there is increased tissue distribution and impaired clearance of the drug.

*HyperTox 3.0* <https://www.ozemail.com.au/-ouad/SALI0001.HTA>

Treat symptomatically.

For exposures involving sulfides and hydrogen sulfide (including gastric acid decomposition products of alkaline sulfides):

- ▶ Hydrogen sulfide anion produces its major toxic effect through inhibition of cytochrome oxidases.
- ▶ Symptoms include profuse salivation, nausea, vomiting and diarrhea. Central nervous effects may include giddiness, headache, vertigo, amnesia, confusion and unconsciousness. Tachypnoea, palpitations, tachycardia, arrhythmia, sweating, weakness and muscle cramps may also indicate overexposure.

Treatment involves:

- ▶ If respirations are depressed, application of artificial respiration, administration of oxygen (continue after spontaneous breathing is established).
- ▶ For severe poisonings administer amyl nitrite and sodium nitrite (as for cyanide poisoning) but omit sodium thiosulfate injection.
- ▶ Atropine sulfate (0.6 mg intramuscularly) may contribute symptomatic relief.
- ▶ Conjunctivitis may be relieved by installation of 1 drop of olive-oil in each eye and sometimes by 3 drops of epinephrine solution (1:1000) at frequent intervals. Occasionally local anesthetics and hot and cold compresses are necessary to control pain.
- ▶ Antibiotics at first hint of pulmonary infection.

[Gosselin et al, *Clinical Toxicology of Commercial Products*]

Hydrogen sulfide is metabolised by oxidation to sulfate, methylation and reaction with metallic ion- or disulfide containing proteins (principally cytochrome c oxidase). This latter reaction is associated with aerobic, cellular respiration and is largely responsible for the toxic effects

for non-steroidal anti-inflammatories (NSAIDs)

- ▶ Symptoms following acute NSAIDs overdoses are usually limited to lethargy, drowsiness, nausea, vomiting, and epigastric pain, which are generally reversible with supportive care. Gastrointestinal bleeding can occur. Hypertension, acute renal failure, respiratory depression, and coma may occur, but are rare. Anaphylactoid reactions have been reported with therapeutic ingestion of NSAIDs, and may occur following an overdose.
- ▶ Patients should be managed by symptomatic and supportive care following a NSAIDs overdose.
- ▶ There are no specific antidotes.
- ▶ Emesis and/or activated charcoal (60 to 100 grams in adults, 1 to 2 g/kg in children), and/or osmotic cathartic may be indicated in patients seen within 4 hours of ingestion with symptoms or following a large overdose (5 to 10 times the usual dose).
- ▶ Forced diuresis, alkalinisation of urine, hemodialysis, or haemoperfusion may not be useful due to high protein binding.

## 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

<b>Fire Incompatibility</b>	None known.
-----------------------------	-------------

### Advice for firefighters

<b>Fire Fighting</b>	<ul style="list-style-type: none"> <li>▶ Alert Fire Brigade and tell them location and nature of hazard.</li> <li>▶ Wear breathing apparatus plus protective gloves in the event of a fire.</li> <li>▶ Prevent, by any means available, spillage from entering drains or water courses.</li> </ul>
----------------------	--

Continued...

## Virbac SEBAZOLE Keratolytic, Keratoplastic, Antibacterial, Antifungal & Antipruritic Wash for Dogs & Cats

	<ul style="list-style-type: none"> <li>▶ Use fire fighting procedures suitable for surrounding area.</li> <li>▶ <b>DO NOT</b> approach containers suspected to be hot.</li> <li>▶ Cool fire exposed containers with water spray from a protected location.</li> <li>▶ If safe to do so, remove containers from path of fire.</li> <li>▶ Equipment should be thoroughly decontaminated after use.</li> </ul>
<b>Fire/Explosion Hazard</b>	<p>The emulsion is not combustible under normal conditions. However, it will break down under fire conditions and the hydrocarbon component will burn.</p> <p>Decomposes on heating and produces toxic fumes of:</p> <ul style="list-style-type: none"> <li>, carbon dioxide (CO<sub>2</sub>)</li> <li>, nitrogen oxides (NO<sub>x</sub>)</li> <li>, sulfur oxides (SO<sub>x</sub>)</li> <li>, other pyrolysis products typical of burning organic material.</li> </ul> <p>May emit poisonous fumes. May emit corrosive fumes.</p>
<b>HAZCHEM</b>	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

<b>Minor Spills</b>	<ul style="list-style-type: none"> <li>▶ Clean up all spills immediately.</li> <li>▶ Avoid breathing vapours and contact with skin and eyes.</li> <li>▶ Control personal contact with the substance, by using protective equipment.</li> <li>▶ Contain and absorb spill with sand, earth, inert material or vermiculite.</li> <li>▶ Wipe up.</li> <li>▶ Place in a suitable, labelled container for waste disposal.</li> </ul>
<b>Major Spills</b>	<p>Moderate hazard.</p> <ul style="list-style-type: none"> <li>▶ Clear area of personnel and move upwind.</li> <li>▶ Alert Fire Brigade and tell them location and nature of hazard.</li> <li>▶ Wear breathing apparatus plus protective gloves.</li> <li>▶ Prevent, by any means available, spillage from entering drains or water course.</li> <li>▶ Stop leak if safe to do so.</li> <li>▶ Contain spill with sand, earth or vermiculite.</li> <li>▶ Collect recoverable product into labelled containers for recycling.</li> <li>▶ Neutralise/decontaminate residue (see Section 13 for specific agent).</li> <li>▶ Collect solid residues and seal in labelled drums for disposal.</li> <li>▶ Wash area and prevent runoff into drains.</li> <li>▶ After clean up operations, decontaminate and launder all protective clothing and equipment before storing and re-using.</li> <li>▶ If contamination of drains or waterways occurs, advise emergency services.</li> </ul>

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

### SECTION 7 HANDLING AND STORAGE

#### Precautions for safe handling

<b>Safe handling</b>	<ul style="list-style-type: none"> <li>▶ <b>DO NOT allow clothing wet with material to stay in contact with skin</b></li> <li>▶ Avoid all personal contact, including inhalation.</li> <li>▶ Wear protective clothing when risk of exposure occurs.</li> <li>▶ Use in a well-ventilated area.</li> <li>▶ Prevent concentration in hollows and sumps.</li> <li>▶ <b>DO NOT enter confined spaces until atmosphere has been checked.</b></li> <li>▶ <b>DO NOT allow material to contact humans, exposed food or food utensils.</b></li> <li>▶ Avoid contact with incompatible materials.</li> <li>▶ <b>When handling, DO NOT eat, drink or smoke.</b></li> <li>▶ Keep containers securely sealed when not in use.</li> </ul>
----------------------	--

Continued...

## Virbac SEBAZOLE Keratolytic, Keratoplastic, Antibacterial, Antifungal & Antipruritic Wash for Dogs & Cats

	<ul style="list-style-type: none"> <li>▶ Avoid physical damage to containers.</li> <li>▶ Always wash hands with soap and water after handling.</li> <li>▶ Work clothes should be laundered separately. Launder contaminated clothing before re-use.</li> <li>▶ Use good occupational work practice.</li> <li>▶ Observe manufacturer's storage and handling recommendations contained within this SDS.</li> <li>▶ Atmosphere should be regularly checked against established exposure standards to ensure safe working conditions are maintained.</li> </ul>
<b>Other information</b>	<ul style="list-style-type: none"> <li>▶ Store in original containers.</li> <li>▶ Keep containers securely sealed.</li> <li>▶ Store in a cool, dry, well-ventilated area.</li> <li>▶ Store away from incompatible materials and foodstuff containers.</li> <li>▶ Protect containers against physical damage and check regularly for leaks.</li> <li>▶ Observe manufacturer's storage and handling recommendations contained within this SDS.</li> </ul>

### Conditions for safe storage, including any incompatibilities

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

## SECTION 8 EXPOSURE CONTROLS / PERSONAL PROTECTION

### Control parameters

#### OCCUPATIONAL EXPOSURE LIMITS (OEL)

#### INGREDIENT DATA

Not Available

#### EMERGENCY LIMITS

Ingredient	Material name	TEEL-1	TEEL-2	TEEL-3
sodium thiosulfate	Sodium thiosulfate pentahydrate	2.4 mg/m <sup>3</sup>	26 mg/m <sup>3</sup>	1,200 mg/m <sup>3</sup>
sodium thiosulfate	Sodium thiosulfate	38 mg/m <sup>3</sup>	410 mg/m <sup>3</sup>	2,500 mg/m <sup>3</sup>
sodium salicylate	Sodium salicylate; (Salicylic acid, sodium salt)	7.1 mg/m <sup>3</sup>	78 mg/m <sup>3</sup>	470 mg/m <sup>3</sup>
sodium lauryl sulfate	Sodium lauryl sulfate	3.9 mg/m <sup>3</sup>	43 mg/m <sup>3</sup>	260 mg/m <sup>3</sup>

Ingredient	Original IDLH	Revised IDLH
sodium thiosulfate	Not Available	Not Available
sodium salicylate	Not Available	Not Available
4-chloro-3,5-xyleneol	Not Available	Not Available
econazole nitrate	Not Available	Not Available
sodium lauryl sulfate	Not Available	Not Available
coconut diethanolamide	Not Available	Not Available
propylene glycol phenyl ether	Not Available	Not Available
Ingredients determined not to be hazardous	Not Available	Not Available

#### MATERIAL DATA

Airborne particulate or vapour must be kept to levels as low as is practicably achievable given access to modern engineering controls and monitoring hardware. Biologically active compounds may produce idiosyncratic effects which are entirely unpredictable on the basis of literature searches and prior clinical experience (both recent and past).

### Exposure controls

<b>Appropriate engineering controls</b>	<p>Enclosed local exhaust ventilation is required at points of dust, fume or vapour generation.</p> <p>HEPA terminated local exhaust ventilation should be considered at point of generation of dust, fumes or vapours.</p> <p>Barrier protection or laminar flow cabinets should be considered for laboratory scale handling.</p> <p>A fume hood or vented balance enclosure is recommended for weighing/ transferring quantities exceeding 500 mg.</p>
---	--

Continued...

## Virbac SEBAZOLE Keratolytic, Keratoplastic, Antibacterial, Antifungal & Antipruritic Wash for Dogs & Cats

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.

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.

### Personal protection



### 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.
- ▶ Face shield. Full face shield may be required for supplementary but never for primary protection of eyes.

## Virbac SEBAZOLE Keratolytic, Keratoplastic, Antibacterial, Antifungal & Antipruritic Wash for Dogs & Cats

	<ul style="list-style-type: none"> <li>▶ Contact lenses may pose a special hazard; soft contact lenses may absorb and concentrate irritants. A written policy document, describing the wearing of lenses or restrictions on use, should be created for each workplace or task. This should include a review of lens absorption and adsorption for the class of chemicals in use and an account of injury experience. Medical and first-aid personnel should be trained in their removal and suitable equipment should be readily available. In the event of chemical exposure, begin eye irrigation immediately and remove contact lens as soon as practicable. Lens should be removed at the first signs of eye redness or irritation - lens should be removed in a clean environment only after workers have washed hands thoroughly. [CDC NIOSH Current Intelligence Bulletin 59], [AS/NZS 1336 or national equivalent]</li> </ul>
<b>Skin protection</b>	See Hand protection below
<b>Hands/feet protection</b>	<p><b>NOTE:</b></p> <ul style="list-style-type: none"> <li>▶ The material may produce skin sensitisation in predisposed individuals. Care must be taken, when removing gloves and other protective equipment, to avoid all possible skin contact.</li> <li>▶ Contaminated leather items, such as shoes, belts and watch-bands should be removed and destroyed.</li> </ul> <p>The selection of suitable gloves does not only depend on the material, but also on further marks of quality which vary from manufacturer to manufacturer. Where the chemical is a preparation of several substances, the resistance of the glove material can not be calculated in advance and has therefore to be checked prior to the application.</p> <p>The exact break through time for substances has to be obtained from the manufacturer of the protective gloves and has to be observed when making a final choice.</p> <p>Personal hygiene is a key element of effective hand care. Gloves must only be worn on clean hands. After using gloves, hands should be washed and dried thoroughly. Application of a non-perfumed moisturizer is recommended.</p> <p>Suitability and durability of glove type is dependent on usage. Important factors in the selection of gloves include:</p> <ul style="list-style-type: none"> <li>· frequency and duration of contact,</li> <li>· chemical resistance of glove material,</li> <li>· glove thickness and</li> <li>· dexterity</li> </ul> <p>Select gloves tested to a relevant standard (e.g. Europe EN 374, US F739, AS/NZS 2161.1 or national equivalent).</p> <ul style="list-style-type: none"> <li>· When prolonged or frequently repeated contact may occur, a glove with a protection class of 5 or higher (breakthrough time greater than 240 minutes according to EN 374, AS/NZS 2161.10.1 or national equivalent) is recommended.</li> <li>· When only brief contact is expected, a glove with a protection class of 3 or higher (breakthrough time greater than 60 minutes according to EN 374, AS/NZS 2161.10.1 or national equivalent) is recommended.</li> <li>· Some glove polymer types are less affected by movement and this should be taken into account when considering gloves for long-term use.</li> <li>· Contaminated gloves should be replaced.</li> </ul> <p>For general applications, gloves with a thickness typically greater than 0.35 mm, are recommended.</p> <p>It should be emphasised that glove thickness is not necessarily a good predictor of glove resistance to a specific chemical, as the permeation efficiency of the glove will be dependent on the exact composition of the glove material. Therefore, glove selection should also be based on consideration of the task requirements and knowledge of breakthrough times.</p> <p>Glove thickness may also vary depending on the glove manufacturer, the glove type and the glove model. Therefore, the manufacturers' technical data should always be taken into account to ensure selection of the most appropriate glove for the task.</p> <p>Note: Depending on the activity being conducted, gloves of varying thickness may be required for specific tasks. For example:</p> <ul style="list-style-type: none"> <li>· Thinner gloves (down to 0.1 mm or less) may be required where a high degree of manual dexterity is needed. However, these gloves are only likely to give short duration protection and would normally be just for single use applications, then disposed of.</li> <li>· Thicker gloves (up to 3 mm or more) may be required where there is a mechanical (as well as a chemical) risk i.e. where there is abrasion or puncture potential</li> </ul> <p>Gloves must only be worn on clean hands. After using gloves, hands should be washed and dried thoroughly. Application of a non-perfumed moisturiser is recommended.</p> <ul style="list-style-type: none"> <li>▶ Rubber gloves (nitrile or low-protein, powder-free latex, latex/ nitrile). Employees allergic to latex gloves should use nitrile gloves in preference.</li> <li>▶ Double gloving should be considered.</li> <li>▶ PVC gloves.</li> <li>▶ Change gloves frequently and when contaminated, punctured or torn.</li> <li>▶ Wash hands immediately after removing gloves.</li> <li>▶ Protective shoe covers. [AS/NZS 2210]</li> <li>▶ Head covering.</li> </ul>
<b>Body protection</b>	See Other protection below
<b>Other protection</b>	<ul style="list-style-type: none"> <li>▶ For quantities up to 500 grams a laboratory coat may be suitable.</li> <li>▶ 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.</li> <li>▶ For quantities over 1 kilogram and manufacturing operations, wear disposable coverall of low permeability and disposable shoe covers.</li> <li>▶ For manufacturing operations, air-supplied full body suits may be required for the provision of advanced respiratory protection.</li> <li>▶ Eye wash unit.</li> <li>▶ Ensure there is ready access to an emergency shower.</li> <li>▶ For Emergencies: Vinyl suit</li> </ul>
<b>Thermal hazards</b>	Not Available

## Virbac SEBAZOLE Keratolytic, Keratoplastic, Antibacterial, Antifungal & Antipruritic Wash for Dogs & Cats

### 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:

Virbac SEBAZOLE Keratolytic, Keratoplastic, Antibacterial, Antifungal & Antipruritic Wash for Dogs & Cats

Material	CPI
BUTYL	C
NATURAL RUBBER	C
NEOPRENE	C
NITRILE	C
NITRILE+PVC	C
PE/EVAL/PE	C
PVA	C
PVC	C
VITON	C
##propylene	glycol

\* 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 AK-P Filter of sufficient capacity. (AS/NZS 1716 & 1715, EN 143:2000 & 149:2001, ANSI Z88 or national equivalent)

Where the concentration of gas/particulates in the breathing zone, approaches or exceeds the "Exposure Standard" (or ES), respiratory protection is required.

Degree of protection varies with both face-piece and Class of filter; the nature of protection varies with Type of filter.

Required Minimum Protection Factor	Half-Face Respirator	Full-Face Respirator	Powered Air Respirator
up to 10 x ES	AK-AUS P2	-	AK-PAPR-AUS / Class 1 P2
up to 50 x ES	-	AK-AUS / Class 1 P2	-
up to 100 x ES	-	AK-2 P2	AK-PAPR-2 P2 ^

^ - Full-face

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(SO<sub>2</sub>), G = Agricultural chemicals, K = Ammonia(NH<sub>3</sub>), 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.

## SECTION 9 PHYSICAL AND CHEMICAL PROPERTIES

### Information on basic physical and chemical properties

<b>Appearance</b>	Clear, blue viscous liquid; mixes with water.		
<b>Physical state</b>	Liquid	<b>Relative density (Water = 1)</b>	1.06-1.11
<b>Odour</b>	Not Available	<b>Partition coefficient n-octanol / water</b>	Not Available
<b>Odour threshold</b>	Not Available	<b>Auto-ignition temperature (°C)</b>	Not Available
<b>pH (as supplied)</b>	Not Available	<b>Decomposition temperature</b>	Not Available
<b>Melting point / freezing point (°C)</b>	Not Available	<b>Viscosity (cSt)</b>	Not Available
<b>Initial boiling point and boiling range (°C)</b>	Not Available	<b>Molecular weight (g/mol)</b>	Not Applicable
<b>Flash point (°C)</b>	Not Applicable	<b>Taste</b>	Not Available
<b>Evaporation rate</b>	Not Available	<b>Explosive properties</b>	Not Available
<b>Flammability</b>	Not Applicable	<b>Oxidising properties</b>	Not Available
<b>Upper Explosive Limit (%)</b>	Not Applicable	<b>Surface Tension (dyn/cm or mN/m)</b>	Not Available
<b>Lower Explosive Limit (%)</b>	Not Applicable	<b>Volatile Component (%vol)</b>	Not Available
<b>Vapour pressure (kPa)</b>	Not Available	<b>Gas group</b>	Not Available
<b>Solubility in water (g/L)</b>	Miscible	<b>pH as a solution (1%)</b>	Not Available

## Virbac SEBAZOLE Keratolytic, Keratoplastic, Antibacterial, Antifungal & Antipruritic Wash for Dogs & Cats

<b>Vapour density (Air = 1)</b>	Not Available	<b>VOC g/L</b>	Not Available
---------------------------------	---------------	----------------	---------------

### SECTION 10 STABILITY AND REACTIVITY

<b>Reactivity</b>	See section 7
<b>Chemical stability</b>	<ul style="list-style-type: none"> <li>▶ Unstable in the presence of incompatible materials.</li> <li>▶ Product is considered stable.</li> <li>▶ Hazardous polymerisation will not occur.</li> </ul>
<b>Possibility of hazardous reactions</b>	See section 7
<b>Conditions to avoid</b>	See section 7
<b>Incompatible materials</b>	See section 7
<b>Hazardous decomposition products</b>	See section 5

### SECTION 11 TOXICOLOGICAL INFORMATION

#### Information on toxicological effects

<b>Inhaled</b>	<p>Evidence shows, or practical experience predicts, that the material produces irritation of the respiratory system, in a substantial number of individuals, following inhalation. In contrast to most organs, the lung is able to respond to a chemical insult by first removing or neutralising the irritant and then repairing the damage. The repair process, which initially evolved to protect mammalian lungs from foreign matter and antigens, may however, produce further lung damage resulting in the impairment of gas exchange, the primary function of the lungs. Respiratory tract irritation often results in an inflammatory response involving the recruitment and activation of many cell types, mainly derived from the vascular system. Not normally a hazard due to non-volatile nature of product</p>
<b>Ingestion</b>	<p>Accidental ingestion of the material may be harmful; animal experiments indicate that ingestion of less than 150 gram may be fatal or may produce serious damage to the health of the individual.</p> <p>Thiosulfate salts are poorly absorbed from the alimentary tract and as a consequence act as an osmotic cathartic. Absorbed thiosulfates are remarkably inert and are distributed in extracellular fluids where they may cause osmotic disturbances.</p> <p>Large oral doses of salicylates may cause mild burning pain in the throat, stomach and usually prompt vomiting. Several hours may elapse before the development of deep and rapid breathing, lassitude, anorexia, nausea, vomiting, thirst and occasional diarrhoea. Common derivatives of salicylic acid produce substantially the same toxic syndrome, ("salicylism"). Major signs and symptoms arise from stimulation and terminal depression of the central nervous system. Stimulation produces vomiting, hyperpnea (abnormal increase in rate and depth of respiration), headache, tinnitus (ringing in the ears) confusion, bizarre behaviour or mania, generalised convulsions. Death is due to respiratory failure or cardiovascular collapse. Severe sensory disturbances such as deafness and dimness of vision are common. Less common features include sweating, skin eruptions, gastrointestinal and other hemorrhages, renal failure and pancreatitis. A tendency to bleed may be manifest by blood in the vomitus (haematemesis), bloody stools (melena) or purplish-red spots (petechiae) on the skin. Many of the toxic effects detailed here are due to or aggravated by severe disturbance of acid-base balance with the chief cause being prolonged hyperventilation from central stimulation. An assessment of acute salicylate intoxication based on dose suggests; 500 mg/kg: Potentially lethal</p> <p>Ingestion of propylene glycol phenyl ethers may cause headache, nausea, light-headedness, drowsiness, incoordination or possible unconsciousness</p> <p>Non-steroidal anti-inflammatory drugs (NSAID) can cause serious gastrointestinal (GI) adverse events including inflammation, bleeding, ulceration, and perforation of the stomach, small intestine, or large intestine, which can be fatal. These serious adverse events can occur at any time, with or without warning symptoms, in patients treated with NSAIDs. Only one in five patients, who develop a serious upper GI adverse event on NSAID therapy, is symptomatic. Upper GI ulcers, gross bleeding, or perforation caused by NSAIDs occur in approximately 1% of patients treated for 3-6 months, and in about 2-4% of patients treated for one year. These trends continue with longer duration of use, increasing the likelihood of developing a serious GI event at some time during the course of therapy.</p> <p>Anaphylactoid (allergic) reactions may occur. This typically occurs in asthmatic patients who experience rhinitis with or without nasal polyps, or who exhibit severe, potentially fatal bronchospasm after taking aspirin or other NSAIDs. NSAIDs, can cause serious skin adverse events such as exfoliative dermatitis, Stevens-Johnson Syndrome (SJS), and toxic epidermal necrolysis (TEN), which can be fatal</p> <p>Non-steroidal anti-inflammatory drug (NSAID) overdose may produce nausea, vomiting, indigestion and epigastric pain. Central nervous system effects may include drowsiness, dizziness, mental confusion, disorientation, lethargy, paraesthesia, numbness, intense headache, blurred vision, tinnitus, decreased auditory acuity, ataxia, muscle twitching, convulsions, stupor and coma. Other reported effects include sweating, oliguria or anuria, tachycardia and hypo- or hypertension. Renal damage may also occur.</p>
<b>Skin Contact</b>	<p>Evidence exists, or practical experience predicts, that the material either produces inflammation of the skin in a substantial number of individuals following direct contact, and/or produces significant inflammation when applied to the healthy intact skin of animals, for up to four hours, such inflammation being present twenty-four hours or more after the end of the exposure period. Skin irritation may also be present after prolonged or repeated exposure; this may result in a form of</p>

Continued...

## Virbac SEBAZOLE Keratolytic, Keratoplastic, Antibacterial, Antifungal & Antipruritic Wash for Dogs & Cats

contact dermatitis (nonallergic). The dermatitis is often characterised by skin redness (erythema) and swelling (oedema) which may progress to blistering (vesiculation), scaling and thickening of the epidermis. At the microscopic level there may be intercellular oedema of the spongy layer of the skin (spongiosis) and intracellular oedema of the epidermis.

The material may accentuate any pre-existing dermatitis condition

One of the mechanisms of skin irritation caused by surfactants is considered to be denaturation of the proteins of skin. It has also been established that there is a connection between the potential of surfactants to denature protein in vitro and their effect on the skin. Nonionic surfactants do not carry any net charge and, therefore, they can only form hydrophobic bonds with proteins. For this reason, proteins are not deactivated by nonionic surfactants, and proteins with poor solubility are not solubilized by nonionic surfactants

Anionic surfactants/ hydrotropes generally produce skin reactions following the removal of natural oils. The skin may appear red and may become sore. Papular dermatitis may also develop. Sensitive individuals may exhibit cracking, scaling and blistering.

Open cuts, abraded or irritated skin should not be exposed to this material

A 30% fatty acid amide (cocoamide DEA solution) was a moderate skin irritant in rabbits. Test sites were scored for irritation according to Draize, and the Primary Irritation Index (PII) was 3.1 (maximum irritation is indicated by the score of 8). In products intended for prolonged contact with the skin, the concentration of cocoamide DEA should not exceed 5%. Fatty acid diethanolamides (C8-C18) and monoethanolamides are classified by CESIO as irritating.

Entry into the blood-stream through, for example, cuts, abrasions, puncture wounds or lesions, may produce systemic injury with harmful effects. Examine the skin prior to the use of the material and ensure that any external damage is suitably protected.

### Eye

When applied to the eye(s) of animals, the material produces severe ocular lesions which are present twenty-four hours or more after instillation.

Some nonionic surfactants may produce a localised anaesthetic effect on the cornea; this may effectively eliminate the warning discomfort produced by other substances and lead to corneal injury. Irritant effects range from minimal to severe dependent on the nature of the surfactant, its concentration and the duration of contact. Pain and corneal damage represent the most severe manifestation of irritation.

Eye contact with the liquid propylene glycol phenyl ether may result in slight irritation and slight corneal injury which should heal in about a week.

Direct eye contact with some concentrated anionic surfactants/ hydrotropes produces corneal damage, in some cases severe. Low concentrations may produce immediate discomfort, conjunctival hyperaemia, and oedema of the corneal epithelium. Healing may take several days. Temporary clouding of the cornea may occur.

Low concentrations (0.6%) of fatty acid amides such as cocoamide DEA are severely irritating to the eyes of rabbits.

Eye contact with fatty acid diethanolamides (C8-18) and fatty acid monoethanolamides may lead to a risk of serious damage to eyes (CESIO)

### Chronic

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

Limited evidence shows that inhalation of the material is capable of inducing a sensitisation reaction in a significant number of individuals at a greater frequency than would be expected from the response of a normal population.

Pulmonary sensitisation, resulting in hyperactive airway dysfunction and pulmonary allergy may be accompanied by fatigue, malaise and aching. Significant symptoms of exposure may persist for extended periods, even after exposure ceases.

Symptoms can be activated by a variety of nonspecific environmental stimuli such as automobile exhaust, perfumes and passive smoking.

There exists limited evidence that shows that skin contact with the material is capable either of inducing a sensitisation reaction in a significant number of individuals, and/or of producing positive response in experimental animals.

There is some evidence that human exposure to the material may result in developmental toxicity. This evidence is based on animal studies where effects have been observed in the absence of marked maternal toxicity, or at around the same dose levels as other toxic effects but which are not secondary non-specific consequences of the other toxic effects.

Mild chronic salicylate intoxication, or "salicylism", may occur after repeated exposures to large doses. Symptoms include dizziness, tinnitus, deafness, sweating, nausea and vomiting, headache and mental confusion. Symptoms of more severe intoxication include hyperventilation, fever, restlessness, ketosis, and respiratory alkalosis and metabolic acidosis.

Depression of the central nervous system may lead to coma, cardiovascular collapse and respiratory failure.

Chronic exposure to the salicylates (o-hydroxybenzoates) may produce metabolic and central system disturbances or damage to the kidneys. Persons with pre-existing skin disorders, eye problems or impaired kidney function may be more susceptible to the effects of these substances. Certain individuals (atopics), notably asthmatics, exhibit significant hypersensitivity to salicylic acid derivatives. Reactions include urticaria and other skin eruptions, rhinitis and severe (even fatal) bronchospasm and dyspnea. Chronic exposure to the p-hydroxybenzoates (parabens) is associated with hypersensitivity reactions following application of these to the skin. Hypersensitivity reactions have also been reported following parenteral or oral administration. Cross-sensitivity occurs between the p-hydroxybenzoates. Hypersensitivity reactions may include by acute bronchospasm, hives (urticaria), deep dermal wheals (angioneurotic oedema), running nose (rhinitis) and blurred vision.

**Virbac SEBAZOLE Keratolytic, Keratoplastic, Antibacterial, Antifungal & Antipruritic Wash for Dogs & Cats**

Anaphylactic shock and skin rash (non- thrombocytopenic purpura) may also occur. Any individual may be predisposed to such anti-body mediated reaction if other chemical agents have caused prior sensitisation (cross-sensitivity).

Sodium lauryl sulfate has been reported to cause pulmonary sensitisation resulting in hyperactive airway dysfunction and pulmonary allergy accompanied by fatigue, malaise and aching. Significant symptoms of exposure can persist for more than two years and can be activated by a variety of non-specific environmental stimuli such as an exhaust, perfumes and passive smoking.

Case studies indicate that ethylene glycol phenyl ether (EGPE), is responsible for acute neurotoxic effects as well as chronic solvent-induced brain syndrome with repeated exposure.

Constant irritability, impaired memory and depression may occur after 1-2 yr occupational exposure to EGPE. Other symptoms include alcohol intolerance, episodes of tachycardia and dyspnea, problems with balance and rash. Woman fish hatchery workers, constantly exposed to EGPE, underwent neurophysiological testing and were found to have persistent focal cognitive impairment.

[Yearbook of Occupational & Environmental Medicine 1991]

Excessive exposure may cause haemolysis, thereby impairing the ability of blood to transport oxygen.

Congeners are expected to exhibit similar behaviour.

Prolonged or repeated skin contact may cause degreasing with drying, cracking and dermatitis following.

NSAIDs may cause an increased risk of serious cardiovascular thrombotic events, myocardial infarction, and stroke, which can be fatal.

NSAIDs cause an increased risk of serious gastrointestinal adverse events including bleeding, ulceration, and perforation of the stomach or intestines, which can be fatal.

These events can occur at any time during use and without warning symptoms.

Prolonged treatment with non-steroidal anti-inflammatory drugs (NSAIDs) has been associated with gastrointestinal irritation, erosion, ulceration, perforation, frank or occult bleeding, diarrhoea, constipation, and blood in the vomit or stool. Kidney damage may result in haematuria (blood in the urine), pyuria (white blood cells in the urine), proteinuria (protein in the urine), urinary casts (cylindrical aggregations of particles that form in the distal nephron, dislodge, and pass into the urine), nocturia (excessive night time urination) , polyuria (production of large volumes of pale urea), dysuria (painful or difficult urination), oliguria (production of abnormally small volumes of urea), or anuria (inability to urinate), renal insufficiency (insufficient excretion of wastes by the kidney), nephrosis and nephrotic syndrome (conditions characterized by oedema and large amounts of protein in the urine and usually increased blood cholesterol), and glomerular and interstitial nephritis. Liver effects, although rare, include jaundice, hepatocellular injury, possible fatal hepatitis, and abnormal liver function tests.

Clinical trials of several COX-2 selective and nonselective NSAIDs of up to three years duration have shown an increased risk of serious cardiovascular (CV) thrombotic events, myocardial infarction, and stroke, which can be fatal. All NSAIDs, both COX-2 selective and nonselective, may have a similar risk.

NSAIDs, can lead to onset of new hypertension or worsening of preexisting hypertension, either of which may contribute to the increased incidence of CV events.

Long-term administration of NSAIDs has resulted in renal papillary necrosis and other renal injury. Acute interstitial nephritis with haematuria, proteinuria, and occasionally nephritic syndrome have been reported.

Anaphylactoid reactions may occur in patients with known prior exposure to other NSAIDs.

NSAIDs have produced ocular changes in animals and there have been reports of adverse eye findings in patients.

Anaemia is sometimes seen in patients receiving NSAIDs.. This may be due to fluid retention, occult or gross GI blood loss, or an incompletely described effect upon erythropoiesis.

In rat studies with NSAIDs, as with other drugs known to inhibit prostaglandin synthesis, an increased incidence of dystocia, delayed parturition, and decreased pup survival occurred.

Because of the known effects of NSAIDs on the foetal cardiovascular system (closure of ductus arteriosus), use during pregnancy (particularly late pregnancy) should be avoided..

NSAIDs inhibit enzymes collectively described as "COXs". In the course of the early search for a specific inhibitor of the negative effects of prostaglandins which spared the positive effects, it was discovered that prostaglandins could indeed be separated into two general classes which could loosely be regarded as "good prostaglandins" and "bad prostaglandins", according to the structure of a particular enzyme involved in their biosynthesis, cyclooxygenase (COX).

Prostaglandins whose synthesis involves the cyclooxygenase-I enzyme, or COX-1, are responsible for maintenance and protection of the gastrointestinal tract, while prostaglandins whose synthesis involves the cyclooxygenase-II enzyme, or COX-2, are responsible for inflammation and pain.

The existing non-steroidal anti-inflammatory drugs (NSAIDs) differ in their relative specificities for COX-2 and COX-1

There has been much concern about the possibility of increased risk for heart attack and stroke in users of NSAID drugs, particularly COX-2 selective NSAIDs. The cardiovascular risks associated with NSAIDs are controversial, with apparently contradictory data produced from different clinical trials and in published meta-analyses. Cardiovascular risk of COX-2 specific inhibitors is not surprising since prostaglandins are involved in regulation of blood pressure by the kidneys.

COX-inhibitors produce blood dyscrasias (abnormal conditions of the blood), and interfere with platelet function.

Phototoxic or photoallergic skin reactions may also occur. Anaphylactoid reactions characterised by maculopapular rash, urticaria, pruritus, bronchospasm, and syncope have been described. Other effects include oedema, metabolic acidosis, hyperkalaemia, azotemia, cystitis and urinary tract infections, visual and hearing disturbances, conjunctivitis, corneal deposits, retinal degeneration, ear pain and occasionally, deafness. Idiosyncratic responses include asthma, allergic interstitial nephritis, hypersensitivity hepatitis, aplastic anaemia and exfoliative dermatitis.

Non-steroidal anti-inflammatory drugs with an inhibitory effect on prostaglandin synthesis, when given during the latter stages of pregnancy, cause premature closure of the foetal ductus arteriosus (1). When given at term they prolong labour and delay parturition. Evidence (1) from animal experimental studies, clinical investigations in humans, and epidemiological studies supports the hypothesis that NSAIDs are chemopreventative agents against colon cancer. This is corroborated by knowledge

## Virbac SEBAZOLE Keratolytic, Keratoplastic, Antibacterial, Antifungal & Antipruritic Wash for Dogs & Cats

of the underlying pathophysiological mechanisms and the effects of arachidonic metabolites, i.e prostaglandins, on the carcinogenic process and the influence of cyclooxygenase (COX) inhibitors such as NSAIDs on these metabolites. 1. Berkel et al; Epidemiol Rev., Vol 18, No. 2, 1996

Because of the known effects of NSAIDs drugs on the foetal cardiovascular system (closure of ductus arteriosus), use during pregnancy (particularly late pregnancy) should be avoided. In rat studies with NSAIDs, as with other drugs known to inhibit prostaglandin synthesis, an increased incidence of dystocia, delayed parturition, and decreased pup survival occurred. Aspirin and NSAIDs may cause anaphylactic or anaphylactoid reactions. Constitutively-expressed cyclooxygenase (COX-1) inhibition is likely to be responsible for the cross-reactions and side effects associated with these drugs, as well as the anaphylactoid reactions sometimes seen in aspirin-sensitive respiratory disease. Though anaphylactic and anaphylactoid reactions may be clinically indistinguishable, they involve different mechanisms. Anaphylactic reactions are due to immediate hypersensitivity involving cross-linking of drug-specific IgE. Regardless of COX selectivity pattern, NSAIDs may function as haptens capable of inducing allergic sensitization. Unlike anaphylaxis, anaphylactoid reactions are most likely related to inhibition of COX-1 by NSAIDs. Thus, an anaphylactoid reaction caused by a particular COX-1 inhibiting NSAID will occur with a chemically unrelated NSAID which also inhibits COX-1 enzymes. Selective COX-2 inhibitors appear to be safe in patients with a history of NSAID-related anaphylactoid reactions but can function as haptens, with resulting sensitisation and anaphylaxis upon next exposure. Eva A Berkes Clinical Reviews in Allergy and Immunology 24, pp 137-147 2003.

COX-2 inhibitors reduce inflammation (and pain) while minimising gastrointestinal adverse drug reactions (e.g. stomach ulcers) that are common with non-selective NSAIDs. COX-1 is involved in synthesis of prostaglandins and thromboxane, but COX-2 is only involved in the synthesis of prostaglandin. Therefore, inhibition of COX-2 inhibits only prostaglandin synthesis without affecting thromboxane and thus has no effect on platelet aggregation or blood clotting.

Chronic abuse of analgesics has been associated with nephropathy. Patients invariably have a history of regular ingestion of substantial or excessive doses over a period of years. In mild cases the condition is reversible. The initial renal lesion is papillary necrosis proceeding to secondary atrophic changes in the renal cortex body. An abnormally high incidence of transitional cell carcinoma of the renal pelvis and bladders has been reported in patients with analgesic nephropathy. Exposure to the material for prolonged periods may cause physical defects in the developing embryo (teratogenesis).

<b>Virbac SEBAZOLE Keratolytic, Keratoplastic, Antibacterial, Antifungal &amp; Antipruritic Wash for Dogs &amp; Cats</b>	<b>TOXICITY</b>	<b>IRRITATION</b>
	Not Available	Not Available
<b>sodium thiosulfate</b>	<b>TOXICITY</b>	<b>IRRITATION</b>
	Dermal (rabbit) LD50: >2000 mg/kg <sup>[1]</sup> Oral (rat) LD50: >2000 mg/kg <sup>[1]</sup>	Not Available
<b>sodium salicylate</b>	<b>TOXICITY</b>	<b>IRRITATION</b>
	Oral (rat) LD50: 930 mg/kg <sup>[2]</sup>	Not Available
<b>4-chloro-3,5-xyleneol</b>	<b>TOXICITY</b>	<b>IRRITATION</b>
	Oral (rat) LD50: 3830 mg/kg <sup>[2]</sup>	Not Available
<b>econazole nitrate</b>	<b>TOXICITY</b>	<b>IRRITATION</b>
	Oral (rat) LD50: 668 mg/kg <sup>[2]</sup>	Eye (rabbit): 1% mild
<b>sodium lauryl sulfate</b>	<b>TOXICITY</b>	<b>IRRITATION</b>
	Dermal (rabbit) LD50: >500 mg/kg <sup>[1]</sup> Oral (rat) LD50: 977 mg/kg <sup>[1]</sup>	Eye (rabbit): 100 mg/24 hr-moderate Skin (human): 25 mg/24 hr - mild
<b>coconut diethanolamide</b>	<b>TOXICITY</b>	<b>IRRITATION</b>
	Inhalation (rat) LC50: 88 ppm/h * <sup>[2]</sup> Oral (rat) LD50: 2700 mg/kg <sup>[2]</sup>	Not Available
<b>propylene glycol phenyl ether</b>	<b>TOXICITY</b>	<b>IRRITATION</b>
	Dermal (rabbit) LD50: >2000 mg/kg <sup>[2]</sup> Oral (rat) LD50: 2830 mg/kg <sup>[2]</sup>	Not Available
<b>Legend:</b>	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	

## Virbac SEBAZOLE Keratolytic, Keratoplastic, Antibacterial, Antifungal & Antipruritic Wash for Dogs & Cats

<b>ECONAZOLE NITRATE</b>	<p>Tremor, convulsions, chronic pulmonary oedema/ congestion, dyspnea, maternal effects, effects on fertility, effects on embryo/ foetus (extra-embryonic structures), foetolethality, specific developmental abnormalities (musculoskeletal system), effects on newborn recorded.</p> <p>for alkyl sulfates; alkane sulfonates and alpha-olefin sulfonates</p> <p>Most chemicals of this category are not defined substances, but mixtures of homologues with different alkyl chain lengths. Alpha-olefin sulfonates are mixtures of alkene sulfonate and hydroxyl alkane sulfonates with the sulfonate group in the terminal position and the double bond, or hydroxyl group, located at a position in the vicinity of the sulfonate group. Common physical and/or biological pathways result in structurally similar breakdown products, and are, together with the surfactant properties, responsible for similar environmental behavior and essentially identical hazard profiles with regard to human health.</p> <p><b>Acute toxicity:</b> These substances are well absorbed after ingestion; penetration through the skin is however poor. After absorption, these chemicals are distributed mainly to the liver.</p> <p>Acute oral LD50 values of alkyl sulfates in rats and/or mice were (in mg/kg):  C10-; 290-580  C10-16-, and C12-; 1000-2000  C12-14, C12-15, C12-16, C12-18 and C16-18-; &gt;2000  C14-18, C16-18-; &gt;5000</p> <p>The clinical signs observed were non-specific (piloerection, lethargy, decreased motor activity and respiratory rate, diarrhoea). At necropsy the major findings were irritation of the gastrointestinal tract and anemia of inner organs. Based on limited data, the acute oral LD50 values of alkane sulfonates and alpha-olefin sulfonates of comparable chain lengths are assumed to be in the same range.</p> <p>The counter ion does not appear to influence the toxicity in a substantial way.</p> <p>Acute dermal LD50 values of alkyl sulfates in rabbits (mg/ kg):  C12-; 200  C12-13 and C10-16-;&gt;500</p> <p>Apart from moderate to severe skin irritation, clinical signs included tremor, tonic-clonic convulsions, respiratory failure, and body weight loss in the study with the C12- alkyl sulfate and decreased body weights after administration of the C10-16- alkyl sulfates. No data are available for alkane sulfonates but due to a comparable metabolism and effect concentrations in long-term studies effect concentrations are expected to be in the same range as found for alkyl sulfates.</p> <p>There are no data available for acute inhalation toxicity of alkyl sulfates, alkane sulfonates or alpha-olefin sulfonates.</p>
<b>SODIUM LAURYL SULFATE</b>	<p>In skin irritation tests using rabbits (aqueous solutions, OECD TG 404):  C8-14 and C8-16 (30%), C12-14 (90%), C14-18 (60%)- corrosive  Under occlusive conditions:  C12, and C12-14 (25%), C12-15-, C13-15 and C15-16 (5-7%) - moderate to strong irritants</p> <p>Comparative studies investigating skin effects like transepidermal water loss, epidermal electrical conductance, skin swelling, extraction of amino acids and proteins or development of erythema in human volunteers consistently showed a maximum of effects with C12-alkyl sulfate, sodium; this salt is routinely used as a positive internal control giving borderline irritant reactions in skin irritation studies performed on humans. As the most irritant alkyl sulfate it can be concluded that in humans 20% is the threshold concentration for irritative effects of alkyl sulfates in general. No data were available with regard to the skin irritation potential of alkane sulfonates. Based on the similar chemical structure they are assumed to exhibit similar skin irritation properties as alkyl sulfates or alpha-olefin sulfonates of comparable chain lengths.</p> <p>In eye irritation tests, using rabbits, C12-containing alkyl sulfates (&gt;10% concentration) were severely irritating and produced irreversible corneal effects. With increasing alkyl chain length, the irritating potential decreases, and C16-18 alkyl sulfate sodium, at a concentration of 25%, was only a mild irritant.</p> <p>Concentrated C14-16- alpha-olefin sulfonates were severely irritating, but caused irreversible effects only if applied as undiluted powder. At concentrations below 10% mild to moderate, reversible effects, were found. No data were available for alkane sulfonates</p> <p>Alkyl sulfates and C14-18 alpha-olefin sulfonates were not skin sensitizers in animal studies. No reliable data were available for alkane sulfonates. Based on the similar chemical structure, no sensitization is expected.</p> <p>However anecdotal evidence suggests that sodium lauryl sulfate causes pulmonary sensitization resulting in hyperactive airway dysfunction and pulmonary allergy accompanied by fatigue, malaise and aching. Significant symptoms of exposure can persist for more than two years and can be activated by a variety of non-specific environmental stimuli such as an exhaust, perfumes and passive smoking.</p> <p>Absorbed sulfonates are quickly distributed through living systems and are readily excreted. Toxic effects may result from the effects of binding to proteins and the ability of sulfonates to translocate potassium and nitrate (NO<sub>3</sub><sup>-</sup>) ions from cellular to interstitial fluids. Airborne sulfonates may be responsible for respiratory allergies and, in some instances, minor dermal allergies. Repeated skin contact with some sulfonated surfactants has produced sensitization dermatitis in predisposed individuals</p> <p><b>Repeat dose toxicity:</b> After repeated oral application of alkyl sulfates with chain lengths between C12 and C18, the liver was the only target organ for systemic toxicity. Adverse effects on this organ included an increase in liver weight, enlargement of liver cells, and elevated levels of liver enzymes. The LOAEL for liver toxicity (parenchymal hypertrophy and</p>

**Virbac SEBAZOLE Keratolytic, Keratoplastic, Antibacterial, Antifungal & Antipruritic Wash for Dogs & Cats**

an increase in comparative liver weight) was 230 mg/kg/day (in a 13 week study with C16-18 alkyl sulfate, sodium). The lowest NOAEL in rats was 55 mg/kg/day (in a 13 week study with C12-alkyl sulfate, sodium). C14- and C14-16-alpha-olefin sulfonates produced NOAELs of 100 mg/kg/day (in 6 month- and 2 year studies). A reduction in body weight gain was the only adverse effect identified in these studies.

No data were available with regard to the repeated dose toxicity of alkane sulfonates. Based on the similarity of metabolic pathways between alkane sulfonates, alkyl sulfates and alkyl-olefin sulfonates, the repeated dose toxicity of alkane sulfonates is expected to be similar with NOAEL and LOAEL values in the same range as for alkyl sulfates and alpha-olefin sulfonates, i.e. 100 and 200-250 mg/kg/day, respectively, with the liver as potential target organ.

**Genotoxicity:** Alkyl sulfates of different chain lengths and with different counter ions were not mutagenic in standard bacterial and mammalian cell systems both in the absence and in the presence of metabolic activation. There was also no indication for a genotoxic potential of alkyl sulfates in various in vivo studies on mice (micronucleus assay, chromosome aberration test, and dominant lethal assay).

alpha-Olefin sulfonates were not mutagenic in the Ames test, and did not induce chromosome aberrations in vitro. No genotoxicity data were available for alkane sulfonates. Based on the overall negative results in the genotoxicity assays with alkyl sulfates and alpha-olefin sulfonates, the absence of structural elements indicating mutagenicity, and the overall database on different types of sulfonates, which were all tested negative in mutagenicity assays, a genotoxic potential of alkane sulfonates is not expected.

**Carcinogenicity:** Alkyl sulfates were not carcinogenic in feeding studies with male and female Wistar rats fed diets with C12-15 alkyl sulfate sodium for two years (corresponding to doses of up to 1125 mg/kg/day).

alpha-Olefin sulfonates were not carcinogenic in mice and rats after dermal application, and in rats after oral exposure.

No carcinogenicity studies were available for the alkane sulfonates.

**Reproductive toxicity:** No indication for adverse effects on reproductive organs was found in various oral studies with different alkyl sulfates. The NOAEL for male fertility was 1000 mg/kg/day for sodium dodecyl sulfate. In a study using alpha-olefin sulfonates in male and female rats, no adverse effects were identified up to 5000 ppm.

**Developmental toxicity:** In studies with various alkyl sulfates (C12 up to C16-18- alkyl) in rats, rabbits and mice, effects on litter parameters were restricted to doses that caused significant maternal toxicity (anorexia, weight loss, and death). The principal effects were higher foetal loss and increased incidences of total litter losses. The incidences of malformations and visceral and skeletal anomalies were unaffected apart from a higher incidence of delayed ossification or skeletal variation in mice at > 500 mg/kg bw/day indicative of a delayed development. The lowest reliable NOAEL for maternal toxicity was about 200 mg/kg/day in rats, while the lowest NOAELs in offspring were 250 mg/kg/day in rats and 300 mg/kg/day for mice and rabbits.

For alpha-olefin sulfonates (C14-16-alpha-olefin sulfonate, sodium) the NOAEL was 600 mg/kg/day both for maternal and developmental toxicity.

No data were available for the reproductive and developmental toxicity of alkane sulfonates. Based on the available data, the similar toxicokinetic properties and a comparable metabolism of the alkyl sulfates and alkane sulfonates, alkane sulfonates are not considered to be developmental toxicants.

Although the database for category members with C<12 is limited, the available data are indicating no risk as the substances have comparable toxicokinetic properties and metabolic pathways. In addition, longer-term studies gave no indication for adverse effects on reproductive organs with different alkyl sulfates

Alkyl sulfates (AS) anionic surfactants are generally classified according to Comité Européen des Agents de Surface et leurs Intermédiaires Organiques (CESIO) as Irritant (Xi) with the risk phrases R38 (Irritating to skin) and R41 (Risk of serious damage to eyes). An exception has been made for C12 AS which is classified as Harmful (Xn) with the risk phrases R22 (Harmful if swallowed) and R38 and R41 (CESIO 2000). AS are not included in Annex 1 of list of dangerous substances of Council Directive 67/548/EEC.

AS are readily absorbed from the gastrointestinal tract after oral administration. Penetration of AS through intact skin appears to be minimal. AS are extensively metabolized in various species resulting in the formation of several metabolites. The primary metabolite is butyric acid-4-sulfate. The major site of metabolism is the liver. AS and their metabolites are primarily eliminated via the urine and only minor amounts are eliminated via the faeces. In rats about 70-90% of the dose was eliminated via the urine within 48 hours after oral, intravenous or intraperitoneal administration of 1 mg of AS per rat. The acute toxicity of AS in animals is considered to be low after skin contact or oral intake.

For a homologous series of AS (C8 to C16), maximum swelling of stratum corneum (the outermost layer of epidermis) of the skin was produced by the C12 homologue. This is in accordance with the fact that the length of the hydrophobic alkyl chain influences the skin irritation potential. Other studies have shown that especially AS of chain lengths C11, C12 and C13 remove most amino acids and soluble proteins from the skin during washing.

Concentrated samples of AS are skin irritants in rabbits and guinea pigs. AS are non-irritant to laboratory animals at a 0.1% concentration. C12 AS is used in research laboratories as a standard substance to irritate skin and has been shown to induce an irritant eczema. AS were found, by many authors, to be the most irritating of the anionic surfactants, although others have judged the alkyl sulfates only as irritant as laurate (fatty acid soap).

A structure/effect relationship with regard to the length of the alkyl chain can also be observed on mucous membranes. The maximum eye irritation occurs at chain lengths of C10 to C14. In acute ocular tests, 10% C12 AS caused corneal damage to the rabbit eyes if not irrigated. Another study showed that a 1.0% aqueous C12 AS solution only had a slight effect on rabbit eyes, whereas 5% C12 AS caused temporary conjunctivitis, and 25% C12 AS resulted in corneal damage.

In a 13-week feeding study, rats were fed dietary levels of 0, 40, 200, 1,000 or 5,000 ppm of C12 AS. The only test material related effect observed was an increase in absolute organ weights in the rats fed with the highest concentration which was 5,000 ppm. The organ weights were not further specified and no other abnormalities were found.

In a mutagenicity study, rats were fed 1.13 and 0.56% C12 AS in the diet for 90 days. This treatment did not cause

## Virbac SEBAZOLE Keratolytic, Keratoplastic, Antibacterial, Antifungal & Antipruritic Wash for Dogs & Cats

chromosomal aberrations in the bone marrow cells.

Mutagenicity studies with *Salmonella typhimurium* strains (Ames test) indicate no mutagenic effects of C12 AS ). The available long-term studies in experimental animals (rats and mice) are inadequate to evaluate the carcinogenic potential of AS.

However, in studies in which animals were administered AS in the diet at levels of up to 4% AS, there was no indication of increased risk of cancer after oral ingestion.

No specific teratogenic effects were observed in rabbits, rats or mice when pregnant animals were dosed with 0.2, 2.0, 300 and 600 mg C12 AS/kg body weight/day by gavage during the most important period of organogenesis (day 6 to 15 of pregnancy for mice and rats and day 6 to 18 of pregnancy for rabbits). Reduced litter size, high incidence of skeletal abnormalities and foetal loss were observed in mice at 600 mg C12 AS/kg/day, a dose level which also caused severe toxic effects in the parent animals in all three species . An aqueous solution of 2% AS was applied (0.1 ml) once daily to the dorsal skin (2 x 3 cm) of pregnant mice from day 1 to day 17 of gestation. A solution of 20% AS was tested likewise from day 1 to day 10 of gestation. The

mice were killed on days 11 and 18, respectively. A significant decrease in the number of implantations was observed when mice were treated with 20% AS compared to a control group which was dosed with water. No evidence of teratogenic effects was noted.

When aqueous solutions of 2% and 20% AS (0.1 ml) were applied once per day to the dorsal skin (2 x 3 cm) of pregnant ICR/Jc1 mice from day 12 to day 17 of gestation no effects on pregnancy outcome were detected. Treatment with 20% AS resulted in growth retardation of suckling mice, but this effect disappeared after weaning. A 10% AS solution (0.1 ml) was applied twice daily to the dorsal skin (2 x 3 cm) of pregnant ICR/Jc1 mice during the preimplantation period (days 0-3 of gestation). A significant number of embryos collected on day 3 as severely deformed or remained at the morula stage. The number of embryos in the oviducts was significantly greater for the mice dosed with AS as compared to the control mice. No pathological changes were detected in the major organs of the dams

**NOTE:** Substance has been shown to be mutagenic in at least one assay, or belongs to a family of chemicals producing damage or change to cellular DNA.

Eye (None) None: None rabbit None 250 ugSkin (rabbit):25 mg/24 hr-moderate Skin (None) None: None rabbit None 50 mg/24Eye (rabbit) 10: mg-

For Fatty Nitrogen Derived (FND) Amides (including several high molecular weight alkyl amino acid amides)

The chemicals in the Fatty Nitrogen Derived (FND) Amides of surfactants are similar to the class in general as to physical/chemical properties, environmental fate and toxicity. Human exposure to these chemicals is substantially documented.

Some typical applications of FND Amides are:

masonry cement additive; curing agent for epoxy resins; closed hydrocarbon systems in oil field production, refineries and chemical plants; and slip and antiblocking additives for polymers.

The safety of the FND Amides to humans is recognised by the U.S. FDA, which has approved stearamide, oleamide and/or erucamide for adhesives; coatings for articles in food contact; coatings for polyolefin films; defoaming agents for manufacture of paper and paperboard; animal glue (defoamer in food packaging); in EVA copolymers for food packaging; lubricants for manufacture of metallic food packaging; irradiation of prepared foods; release agents in manufacture of food packaging materials, food contact surface of paper and paperboard; cellophane in food packaging; closure sealing gaskets; and release agents in polymeric resins and petroleum wax. The low order of toxicity indicates that the use of FND Amides does not pose a significant hazard to human health.

The differences in chain length, degree of saturation of the carbon chains, source of the natural oils, or addition of an amino group in the chain would not be expected to have an impact on the toxicity profile. This conclusion is supported by a number of studies in the FND family of chemicals (amines, cationics, and amides as separate categories) that show no differences in the length or degree of saturation of the alkyl substituents and is also supported by the limited toxicity of these long-chain substituted chemicals

The Fatty nitrogen-derived amides (FND amides) comprise four categories:

- Subcategory I: Substituted Amides
- Subcategory II: Fatty Acid Reaction Products with Amino Compounds (Note: Subcategory II chemicals, in many cases, contain Subcategory I chemicals as major components)
- Subcategory III: Imidazole Derivatives
- Subcategory IV: FND Amphoterics

**Acute Toxicity:** The low acute oral toxicity of the FND Amides is well established across all Subcategories by the available data. The limited acute toxicity of these chemicals is also confirmed by four acute dermal and two acute inhalation studies

**Repeated Dose and Reproductive Toxicity:** Two subchronic toxicity studies demonstrating low toxicity are available for Subcategory I chemicals. In addition, a 5-day repeated dose study for a third chemical confirmed the minimal toxicity of these chemicals. Since the Subcategory I chemicals are major components of many Subcategory II chemicals, and based on the low repeat-dose toxicity of the amino compounds (e.g. diethanolamine, triethanolamine) used for producing the Subcategory II derivatives, the Subcategory I repeat-dose toxicity studies adequately support Subcategory II.

Two subchronic toxicity studies in Subcategory III confirmed the low order of repeat dose toxicity for the FND Amides Imidazole derivatives. For Subcategory IV, two subchronic toxicity studies for one of the chemicals indicated a low order of repeat-dose toxicity for the FND amphoteric salts similar to that seen in the other categories.

**Genetic Toxicity in vitro:** Based on the lack of effect of one or more chemicals in each subcategory, adequate data for mutagenic activity as measured by the *Salmonella* reverse mutation assay exist for all of the subcategories.

**Developmental Toxicity:** A developmental toxicity study in Subcategory I and in Subcategory IV and a third study for a chemical in Subcategory III are available. The studies indicate these chemicals are not developmental toxicants, as expected based on their structures, molecular weights, physical properties and knowledge of similar chemicals. As above for repeat-dose toxicity, the data for Subcategory I are adequate to support Subcategory II.

In evaluating potential toxicity of the FND Amides chemicals, it is also useful to review the available data for the related FND Cationic and FND Amines Category chemicals. Acute oral toxicity studies (approximately 80 studies for 40 chemicals in the three categories) provide LD50 values from approximately 400 to 10,000 mg/kg with no apparent organ specific toxicity. Similarly, repeated dose toxicity studies (approximately 35 studies for 15 chemicals) provide NOAELs between 10 and 100 mg/kg/day for rats and slightly lower for dogs. More than 60 genetic toxicity studies (*in vitro* bacterial and

### COCONUT DIETHANOLAMIDE

**Virbac SEBAZOLE Keratolytic, Keratoplastic, Antibacterial, Antifungal & Antipruritic Wash for Dogs & Cats**

mammalian cells as well as *in vivo* studies) indicated no mutagenic activity among more than 30 chemicals tested. For reproductive evaluations, 14 studies evaluated reproductive endpoints and/or reproductive organs for 11 chemicals, and 15 studies evaluated developmental toxicity for 13 chemicals indicating no reproductive or developmental effects for the FND group as a whole.

The material may produce severe irritation to the eye causing pronounced inflammation. Repeated or prolonged exposure to irritants may produce conjunctivitis.

for diethanolamine (DEA):

In animal studies, DEA has low acute toxicity via the oral and dermal routes with moderate skin irritation and severe eye irritation. In subchronic toxicity testing conducted via the oral route in rats and mice, the main effects observed were increased organ weights and histopathology of the kidney and/or liver, with the majority of other tissue effects noted only at relatively high dosages. In subchronic studies conducted via the dermal route, skin irritation was noted as well as systemic effects similar to those observed in the oral studies. DEA has not been shown to be mutagenic or carcinogenic in rats; however, there is evidence of its carcinogenicity in mice.

**Subchronic toxicity:** The subchronic toxicity of DEA has been studied in F344 rats and B6C3F1 mice by exposure through drinking water or dermal administration, in 2 week and 13 week studies.

Target organs for toxicity included blood, kidney, brain and spinal cord, seminiferous tubules and dermal application site in rats and liver, kidney, heart, salivary gland and dermal application site in mice. Effects on seminiferous tubules were accompanied by reductions in sperm count and reduced sperm motility. Hematological evaluations indicated normochromic, microcytic anemia in the dermal study in male rats (NOEL = 32 mg/kg) and females (LOEL = 32 mg/kg). Anemia was also observed in rats in the drinking water study with a LOEL of 14 mg/kg/d in females and a LOEL of 48 mg/kg/d in males for altered hematological parameters. These findings were similar to those observed in the 2 week studies, but the magnitude of the changes was greater in the 13 week studies. Hematological parameters were normal in controls. No associated histopathological changes were noted in femoral bone marrow. Haematological parameters were not evaluated in mice.

**Developmental toxicity:** In a developmental toxicity study conducted via the oral route, effects of concern were observed only in the presence of maternal toxicity. In a developmental toxicity study conducted via the dermal route using two species of mammals, developmental toxicity was observed only in one species and only at doses causing significant maternal toxicity. Metabolically, DEA is excreted largely unchanged in the urine.

**Carcinogenicity:** A two-year dermal cancer study bioassay results on DEA and three fatty acid condensates of DEA indicated that liver tumours occurred in male and female mice exposed to DEA and two of the condensates. In addition kidney tumours occurred in male mice exposed to DEA and one of the condensates. Compelling evidence suggested that the toxicity observed in mice and rats treated with the DEA condensates was associated with free DEA and not with other components of the condensates. A weight of evidence analysis of data relevant to the assessment of the liver and kidney tumours in mice resulted in the conclusion that these tumours are not relevant to humans under the expected conditions of exposure and that liver and kidney toxicity should be evaluated on a threshold basis. This conclusion is based on the following:

- ▶ DEA is not genotoxic
- ▶ tumour development occurred at doses also associated with chronic hyperplasia
- ▶ there was no dose-related increase in malignancy, multiplicity of tumours or decrease in latency period
- ▶ tumours occurred late in life
- ▶ tumour response was species-specific (only mice were affected, not rats)
- ▶ tumour response was sex-specific (only male mice were affected, not females)
- ▶ tumour development was site-specific, with only liver and kidney affected, both sites of DEA accumulation;
- ▶ there was no tumour response in skin, despite evidence of chronic dermal toxicity
- ▶ there is a plausible mechanism, supported by various data, to explain the renal toxicity of DEA
- ▶ data support threshold mechanisms of renal carcinogenesis for a number of non-genotoxic chemicals
- ▶ the exposure regime used in the mouse study (*i.e.*, lifetime continuous exposure to DEA in ethanol vehicle at doses causing chronic dermal toxicity) is not relevant to human exposure (exposure through cosmetic vehicles with daily removal, under non-irritating conditions).

In considering the aggregate data on a DEA basis from the four studies using DEA and related condensates, the NOEL for kidney toxicity was 19 mg/kg/d, which resulted from a dose of 100 mg/kg/d of cocamide DEA containing 19% free DEA.

**Anaemia:** Rats exposed to DEA condensates developed anaemia. This was considered to be of to be relevant for humans since anaemia in rodents and humans share common etiologies. The proposed mechanism by which DEA could cause anemia involves disruption of phospholipid metabolism leading to membrane perturbation and functional change to erythrocytes. Some doubt about the relevance of the findings arises because ethanol was used as the vehicle in the dermal studies, and ethanol is known to cause anaemia in rodents through a mechanism involving membrane disruption. The possibility of a synergistic or additive role for DEA and ethanol in combination cannot be ruled out.

In considering the aggregate data on a DEA basis from the four 13-week dermal studies using DEA and related condensates, the NOEL for microcytic anemia was 9.5 mg/kg/d, which resulted from a dose of 50 mg/kg/d of cocamide DEA containing 19% free DEA.

The NOELs for mice and rats derived in this hazard assessment were as follows:

Anaemia in rats: 9.5 mg/kg/d (based on microcytic anemia)

Organ toxicity in mice: 2.2 mg/kg/d (based on liver toxicity)

In extrapolating among species for the purposes of risk assessment, the prime consideration with respect to dermally applied DEA was differential dermal absorption. Evidence indicates that dermal penetration of DEA is greatest in mice and lower in rats and humans. Interspecies extrapolation was accomplished in this assessment by converting applied doses to bioavailable doses (*i.e.*, internal doses) using dermal bioavailability determined in studies with rats and mice *in vivo*, so as to be able to compare these with internal doses expected to be experienced by humans through use of personal care products.

Based on measured bioavailability in mice and rats, the bioavailable NOELs corresponding to the foregoing were:

Anaemia in rats: 0.8 mg/kg/d (based on microcytic anemia)

Organ toxicity in mice: 0.55 mg/kg/d (based on liver toxicity)

## Virbac SEBAZOLE Keratolytic, Keratoplastic, Antibacterial, Antifungal & Antipruritic Wash for Dogs & Cats

**Kidney toxicity:** Effects on the kidney were observed in rats treated with DEA in drinking water or by dermal exposure after as little as 2 weeks of exposure. Effects included renal tubule hyperplasia, renal tubular epithelial necrosis, renal tubule mineralization and increased relative organ weight. Similar changes were observed after 13 weeks of exposure of rats to DEA in drinking water and by dermal administration. The NOEL in male rats was 250 mg/kg/d in the dermal study, while in female rats renal tubule mineralisation was observed at the lowest dose of 32 mg/kg/d. After 2 years of dermal exposure there were no histopathological changes in the kidneys of male rats given doses of up to 64 mg/kg/d. In females, there were no significant increases in the incidences of renal tubule epithelial necrosis, hyperplasia or mineralisation as was observed after 13 weeks of exposure, however, there was an increase in the severity and incidence of nephropathy. This was the result of a treatment-related exacerbation of a previously existing lesion, since the incidence in controls was 80%, increasing to 94-96% in treated groups. There was no significant increase in the incidence of kidney tumours in rats treated with DEA or any of the condensates in 2-year dermal studies.

**Liver toxicity:** Effects on liver, including increases in relative organ weight and histopathological changes were observed in male and female mice in the 2 week drinking water study with DEA. Increases in liver weight were observed in the two week dermal study, but were not associated with histopathological changes. After 13 weeks of exposure, relative liver weights were increased compared to controls in male and female rats, with no associated histopathology. There is some doubt about whether these changes in liver weights were of toxicological significance, since there was no associated histopathology, the dose-response was not consistent and there were no effects on liver in the 2 year study in rats.

In the study with coconut diethanolamide (CDEA) (100 and 200 mg/kg/d) in which 19% of the applied dose was DEA, there were no liver effects in rats after 13 weeks or 2 years of dermal exposure. No liver toxicity in rats was observed in the 2 year dermal studies of lauramide or oleamide DEA

Fatty acid amides (FAA) are ubiquitous in household and commercial environments. The most common of these are based on coconut oil fatty acids alkanolamides. These are the most widely studied in terms of human exposure.

Fatty acid diethanolamides (C8-C18) are classified by Comité Européen des Agents de Surface et de leurs Intermediaires Organiques (CESIO) as Irritating (Xi) with the risk phrases R38 (Irritating to skin) and R41 (Risk of serious damage to eyes). Fatty acid monoethanolamides are classified as Irritant (Xi) with the risk phrases R41

Several studies of the sensitization potential of cocoamide diethanolamide (DEA) indicate that this FAA induces occupational allergic contact dermatitis and a number of reports on skin allergy patch testing of cocoamide DEA have been published. These tests indicate that allergy to cocoamide DEA is becoming more common.

Alkanolamides are manufactured by condensation of diethanolamine and the methylester of long chain fatty acids. Several alkanolamides (especially secondary alkanolamides) are susceptible to nitrosamine formation which constitutes a potential health problem. Nitrosamine contamination is possible either from pre-existing contamination of the diethanolamine used to manufacture cocoamide DEA, or from nitrosamine formation by nitrosating agents in formulations containing cocoamide DEA. According to the Cosmetic Directive (2000) cocoamide DEA must not be used in products with nitrosating agents because of the risk of formation of N-nitrosamines. The maximum content allowed in cosmetics is 5% fatty acid dialkanolamides, and the maximum content of N-nitrosodialkanolamines is 50 mg/kg. The preservative 2-bromo-2-nitropropane-1,3-diol is a known nitrosating agent for secondary and tertiary amines or amides. Model assays have indicated that 2-bromo-2-nitropropane-1,3-diol may lead to the N-nitrosation of diethanolamine forming the carcinogenic compound, N-nitrosodiethanolamine which is a potent liver carcinogen in rats (IARC 1978).

Several FAAs have been tested in short-term genotoxicity assays. No indication of any potential to cause genetic damage was seen. Lauramide DEA was tested in mutagenicity assays and did not show mutagenic activity in *Salmonella typhimurium* strains or in hamster embryo cells. Cocoamide DEA was not mutagenic in strains of *Salmonella typhimurium* when tested with or without metabolic activation

Environmental and Health Assessment of Substances in Household Detergents and Cosmetic Detergent Products, Environment Project, 615, 2001. Miljøministeriet (Danish Environmental Protection Agency)

**WARNING:** This substance has been classified by the IARC as Group 2B: Possibly Carcinogenic to Humans.

In a study of dermal application in mice, coconut oil diethanolamine condensate (coconut diethanolamide) increased the incidence of hepatocellular carcinoma and hepatocellular adenoma in males and females, and of hepatoblastoma in males. The incidence of renal tubule adenoma and carcinoma combined was also increased in males. In a study of dermal application in rats, no increase in tumour incidence was observed.

Tumours of the kidney and hepatoblastoma are rare spontaneous neoplasms in experimental animals.

The carcinogenic effects of the coconut oil diethanolamine condensate used in the cancer bioassay may be due to the levels of diethanolamine (18.2%) in the solutions tested.

Mechanistic data are very weak to evaluate the carcinogenic potential of coconut oil diethanolamine condensate per se

According to IARC:

Coconut oil diethanolamine condensate is possibly carcinogenic to humans (Group 2B)

\*Ethyquad C/12 SDS

No significant acute toxicological data identified in literature search.

Propylene glycol phenyl ether (PPH) is rapidly absorbed, distributed throughout the body, metabolized, and eliminated after oral administration. The major routes of elimination are via the urine and feces. The types of metabolites are parent ether conjugates, hydrolysed propylene glycol, and hydrolysed alcohol (phenol) conjugates. Propylene glycol phenyl ether exhibits low acute toxicity by the oral, and inhalation routes. The oral LD50 in rats exceeds 2000 mg/kg (1 death from 10 subjects occurred at this highest dose tested); and the 4-hour inhalation LC50 in rats was greater than 5400 mg/m<sup>3</sup> (no deaths). PPH was severely irritating to the eyes but non-irritating to skin in rabbits tested and evaluated according to the Draize criteria.

### PROPYLENE GLYCOL PHENYL ETHER

**Virbac SEBAZOLE Keratolytic, Keratoplastic, Antibacterial, Antifungal & Antipruritic Wash for Dogs & Cats**

PPh did not cause skin sensitization when tested with guinea pigs by the Buehler method.

In repeated dose-studies ranging in duration from 4 to 26 weeks, few adverse effects were found even at high exposure levels and effects that did occur were mild in nature. In one study, PPh was administered to two generations of rats (25/sex/group) in drinking water for 26 weeks at concentrations of 0, 100, 1000, or 5000 ppm (equivalent to doses of 0, 11.3, 113, or 478 mg/kg-d) (this was a 2-generation reproductive toxicity study also discussed below). Effects were seen only at the highest exposure concentration that manifested as reduced body weights and corresponding reduced food and water consumption. No clinical signs were evident during the course of exposure and no gross or histopathological lesions were seen at autopsy. The NOAEL for this drinking water study with rats was 1000 ppm (113 mg/kg-d) and the LOAEL was 5000 ppm (478 mg/kg-day), based on body weight changes. In another repeated dose test, this time by the dermal route of exposure, rabbits (5/sex/group) received daily applications of PPh 5 days/week for four weeks (19 total applications). A slight increase in platelet counts was found that reached statistical significance in males at the high dose level. Platelet counts in females were unaltered at any dose level. No other parameters were affected other than a local thickening of the skin at the site of application. The increased platelet count in males was considered spurious since no other hematological or clinical chemistry (or any other) parameters corroborated this finding. Thus, the systemic toxicity NOAEL for PPh by the dermal route of exposure in rabbits was the highest dose tested of 1000 mg/kg-day. In the two-generation reproductive toxicity study discussed above (rats 25 pairs/generation) treated orally with 0, 100, 1000, or 5000 ppm PPh in drinking water, no adverse effects were found on fertility, reproductive performance, or on reproductive tissues in parental generations. In offspring, reduced pup weights as well as decreased relative spleen weights and increased relative brain weights and retarded sexual maturation were found at the high dose (but with no effect on reproductive parameters in the F1 generation once they reached sexual maturity). In a developmental toxicity study, PPh was administered daily by gavage to pregnant rabbits (15 per group) over the period of organogenesis at doses of 0, 60, 180, or 540 mg/kg-day. In the dams, the high dose of PPh caused decreased food consumption, decreased body weights, and prostration. No maternal toxicity was seen at the lower dose levels. In fetuses, a statistical increase in the rate of total soft tissue variations was detected (septal heart defect) in the medium and high dose groups. It is possible that this may be considered coincidental because of the low incidence (1 fetus in each group), the common spontaneous occurrence of the variation in this strain of rabbit, and because statistical significance was conferred only due to the unusually low level in the concurrent control group (2.2% fetal incidence and 7.1% litter incidence versus 7.7% and 30.2%, respectively, in the laboratory historical controls). With regard to skeletal variations (predominantly an increase in 13th ribs when combined with other skeletal variations), a statistical increase was detected in the high dose group. This increase in skeletal variations was considered treatment related because the incidence (approximately 10%) exceeded historical control levels. The NOAEL for maternal toxicity was 180 mg/kg-day and the LOAEL was 540 mg/kg-day, based on reduced body weight and clinical signs. The NOAEL for fetal toxicity was 180 mg/kg-day and the LOAEL was 540 mg/kg-day based on the increased incidence of 13th rib buds. PPh exhibits toxicity in the developing rabbit conceptus at high doses that produce toxicity in the dam.

PPh tested negative in the Ames Salmonella assay and also was negative in an *in vitro* chromosome aberration study with human lymphocytes. In an *in vivo* mouse bone marrow micronucleus test, mice received two consecutive daily doses of 0, 500, 1000, or 2000 mg/kg-day. The high dose animals had a slightly increased incidence of micronuclei that reached statistical significance in a first assay but did not in a second (although a trend was evident). The study authors attributed this finding to hypothermia, which occurred only in the high dose animals and which has been shown with other chemicals to cause increased micronuclei as a secondary effect from hypothermia. It seems reasonable to conclude that the negative *in vitro* results and the equivocal *in vivo* results at a very high dose level that may be due to physiological stress indicate that propylene glycol phenyl ether does not pose a genotoxicity hazard at doses that would likely be encountered in the environment. PPh has not been tested for carcinogenicity

For ethylene glycol monoalkyl ethers and their acetates (EGMAEs):

Typical members of this category are ethylene glycol propylene ether (EGPE), ethylene glycol butyl ether (EGBE) and ethylene glycol hexyl ether (EGHE) and their acetates.

EGMAEs are substrates for alcohol dehydrogenase isozyme ADH-3, which catalyzes the conversion of their terminal alcohols to aldehydes (which are transient metabolites). Further, rapid conversion of the aldehydes by aldehyde dehydrogenase produces alkoxyacetic acids, which are the predominant urinary metabolites of mono substituted glycol ethers.

**Acute Toxicity:** Oral LD50 values in rats for all category members range from 739 (EGHE) to 3089 mg/kg bw (EGPE), with values increasing with decreasing molecular weight. Four to six hour acute inhalation toxicity studies were conducted for these chemicals in rats at the highest vapour concentrations practically achievable. Values range from LC0 > 85 ppm (508 mg/m<sup>3</sup>) for EGHE, LC50 > 400ppm (2620 mg/m<sup>3</sup>) for EGBEA to LC50 > 2132 ppm (9061 mg/m<sup>3</sup>) for EGPE. No lethality was observed for any of these materials under these conditions. Dermal LD50 values in rabbits range from 435 mg/kg bw (EGBE) to 1500 mg/kg bw (EGBEA). Overall these category members can be considered to be of low to moderate acute toxicity. All category members cause reversible irritation to skin and eyes, with EGBEA less irritating and EGHE more irritating than the other category members. EGPE and EGBE are not sensitizers in experimental animals or humans. Signs of acute toxicity in rats, mice and rabbits are consistent with haemolysis (with the exception of EGHE) and non-specific CNS depression typical of organic solvents in general. Alkoxyacetic acid metabolites, propoxyacetic acid (PAA) and butoxyacetic acid (BAA), are responsible for the red blood cell hemolysis. Signs of toxicity in humans deliberately ingesting cleaning fluids containing 9-22% EGBE are similar to those of rats, with the exception of haemolysis. Although decreased blood haemoglobin and/or haemoglobinuria were observed in some of the human cases, it is not clear if this was due to haemolysis or haemodilution as a result of administration of large volumes of fluid. Red blood cells of humans are many-fold more resistant to toxicity from EGPE and EGBE *in vitro* than those of rats.

**Repeat dose toxicity:** The fact that the NOAEL for repeated dose toxicity of EGBE is less than that of EGPE is consistent with red blood cells being more sensitive to EGBE than EGPE. Blood from mice, rats, hamsters, rabbits and baboons were sensitive to the effects of BAA *in vitro* and displayed similar responses, which included erythrocyte swelling (increased haematocrit and mean corpuscular hemoglobin), followed by hemolysis. Blood from humans, pigs, dogs, cats, and guinea pigs was less sensitive to haemolysis by BAA *in vitro*.

**Mutagenicity:** In the absence and presence of metabolic activation, EGBE tested negative for mutagenicity in Ames tests conducted in *S. typhimurium* strains TA97, TA98, TA100, TA1535 and TA1537 and EGHE tested negative in strains TA98, TA100, TA1535, TA1537 and TA1538. *In vitro* cytogenetic and sister chromatid exchange assays with EGBE and EGHE in Chinese Hamster Ovary Cells with and without metabolic activation and *in vivo* micronucleus tests with EGBE in rats and

**Virbac SEBAZOLE Keratolytic, Keratoplastic, Antibacterial, Antifungal & Antipruritic Wash for Dogs & Cats**

mice were negative, indicating that these glycol ethers are not genotoxic.

**Carcinogenicity:** In a 2-year inhalation chronic toxicity and carcinogenicity study with EGBE in rats and mice a significant increase in the incidence of liver haemangiosarcomas was seen in male mice and forestomach tumours in female mice. It was decided that based on the mode of action data available, there was no significant hazard for human carcinogenicity

**Reproductive and developmental toxicity.** The results of reproductive and developmental toxicity studies indicate that the glycol ethers in this category are not selectively toxic to the reproductive system or developing fetus, developmental toxicity is secondary to maternal toxicity. The repeated dose toxicity studies in which reproductive organs were examined indicate that the members of this category are not associated with toxicity to reproductive organs (including the testes). Results of the developmental toxicity studies conducted via inhalation exposures during gestation periods on EGPE (rabbits -125, 250, 500 ppm or 531, 1062, or 2125 mg/m<sup>3</sup> and rats - 100, 200, 300, 400 ppm or 425, 850, 1275, or 1700 mg/m<sup>3</sup>), EGBE (rat and rabbit - 25, 50, 100, 200 ppm or 121, 241, 483, or 966 mg/m<sup>3</sup>), and EGHE (rat and rabbit - 20.8, 41.4, 79.2 ppm or 124, 248, or 474 mg/m<sup>3</sup>) indicate that the members of the category are not teratogenic.

The NOAELs for developmental toxicity are greater than 500 ppm or 2125 mg/m<sup>3</sup> (rabbit-EGPE), 100 ppm or 425 mg/m<sup>3</sup> (rat-EGPE), 50 ppm or 241 mg/m<sup>3</sup> (rat EGBE) and 100 ppm or 483 mg/m<sup>3</sup> (rabbit EGBE) and greater than 79.2 ppm or 474 mg/m<sup>3</sup> (rat and rabbit-EGHE).

for propylene glycol ethers (PGEs):

Typical propylene glycol ethers include propylene glycol n-butyl ether (PnB); dipropylene glycol n-butyl ether (DPnB); dipropylene glycol methyl ether acetate (DPMA); tripropylene glycol methyl ether (TPM).

Testing of a wide variety of propylene glycol ethers. Testing of a wide variety of propylene glycol ethers has shown that propylene glycol-based ethers are less toxic than some ethers of the ethylene series. The common toxicities associated with the lower molecular weight homologues of the ethylene series, such as adverse effects on reproductive organs, the developing embryo and fetus, blood (haemolytic effects), or thymus, are not seen with the commercial-grade propylene glycol ethers. In the ethylene series, metabolism of the terminal hydroxyl group produces an alkoxyacetic acid. The reproductive and developmental toxicities of the lower molecular weight homologues in the ethylene series are due specifically to the formation of methoxyacetic and ethoxyacetic acids.

Longer chain length homologues in the ethylene series are not associated with the reproductive toxicity but can cause haemolysis in sensitive species, also through formation of an alkoxyacetic acid. The predominant alpha isomer of all the PGEs (thermodynamically favored during manufacture of PGEs) is a secondary alcohol incapable of forming an alkoxypropionic acid. In contrast beta-isomers are able to form the alkoxypropionic acids and these are linked to teratogenic effects (and possibly haemolytic effects).

This alpha isomer comprises greater than 95% of the isomeric mixture in the commercial product.

Because the alpha isomer cannot form an alkoxypropionic acid, this is the most likely reason for the lack of toxicity shown by the PGEs as distinct from the lower molecular weight ethylene glycol ethers. More importantly, however, very extensive empirical test data show that this class of commercial-grade glycol ether presents a low toxicity hazard. PGEs, whether mono, di- or tripropylene glycol-based (and no matter what the alcohol group), show a very similar pattern of low to non-detectable toxicity of any type at doses or exposure levels greatly exceeding those showing pronounced effects from the ethylene series. One of the primary metabolites of the propylene glycol ethers is propylene glycol, which is of low toxicity and completely metabolised in the body.

As a class, the propylene glycol ethers are rapidly absorbed and distributed throughout the body when introduced by inhalation or oral exposure. Dermal absorption is somewhat slower but subsequent distribution is rapid. Most excretion for PGEs is via the urine and expired air. A small portion is excreted in the faeces.

As a group PGEs exhibits low acute toxicity by the oral, dermal, and inhalation routes. Rat oral LD50s range from >3,000 mg/kg (PnB) to >5,000 mg/kg (DPMA). Dermal LD50s are all > 2,000 mg/kg (PnB, & DPnB; where no deaths occurred), and ranging up to >15,000 mg/kg (TPM). Inhalation LC50 values were higher than 5,000 mg/m<sup>3</sup> for DPMA (4-hour exposure), and TPM (1-hour exposure). For DPnB the 4-hour LC50 is >2,040 mg/m<sup>3</sup>. For PnB, the 4-hour LC50 was >651 ppm (>3,412 mg/m<sup>3</sup>), representing the highest practically attainable vapor level. No deaths occurred at these concentrations. PnB and TPM are moderately irritating to eyes while the remaining category members are only slightly irritating to nonirritating. PnB is moderately irritating to skin while the remaining category members are slightly to non-irritating. None are skin sensitizers.

In repeated dose studies ranging in duration from 2 to 13 weeks, few adverse effects were found even at high exposure levels and effects that did occur were mild in nature. By the oral route of administration, NOAELs of 350 mg/kg-d (PnB – 13 wk) and 450 mg/kg-d (DPnB – 13 wk) were observed for liver and kidney weight increases (without accompanying histopathology). LOAELs for these two chemicals were 1000 mg/kg-d (highest dose tested).

Dermal repeated-dose toxicity tests have been performed for many PGEs. For PnB, no effects were seen in a 13-wk study at doses as high as 1,000 mg/kg-d. A dose of 273 mg/kg-d constituted a LOAEL (increased organ weights without histopathology) in a 13-week dermal study for DPnB. For TPM, increased kidney weights (no histopathology) and transiently decreased body weights were found at a dose of 2,895 mg/kg-d in a 90-day study in rabbits. By inhalation, no effects were observed in 2-week studies in rats at the highest tested concentrations of 3244 mg/m<sup>3</sup> (600 ppm) for PnB and 2,010 mg/m<sup>3</sup> (260 ppm) for DPnB. TPM caused increased liver weights without histopathology by inhalation in a 2-week study at a LOAEL of 360 mg/m<sup>3</sup> (43 ppm). In this study, the highest tested TPM concentration, 1010 mg/m<sup>3</sup> (120 ppm), also caused increased liver weights without accompanying histopathology. Although no repeated-dose studies are available for the oral route for TPM, or for any route for DPMA, it is anticipated that these chemicals would behave similarly to other category members. One and two-generation reproductive toxicity testing has been conducted in mice, rats, and rabbits via the oral or inhalation routes of exposure on PM and PMA. In an inhalation rat study using PM, the NOAEL for parental toxicity is 300 ppm (1106 mg/m<sup>3</sup>) with decreases in body and organ weights occurring at the LOAEL of 1000 ppm (3686 mg/m<sup>3</sup>). For offspring toxicity the NOAEL is 1000 ppm (3686 mg/m<sup>3</sup>), with decreased body weights occurring at 3000 ppm (11058 mg/m<sup>3</sup>). For PMA, the NOAEL for parental and offspring toxicity is 1000 mg/kg/d. in a two generation gavage study in rats. No adverse effects were found on reproductive organs, fertility rates, or other indices commonly monitored in such studies. In addition, there is no evidence from histopathological data from repeated-dose studies for the category members that would indicate that these chemicals would pose a reproductive hazard to human health.

In developmental toxicity studies many PGEs have been tested by various routes of exposure and in various species at significant exposure levels and show no frank developmental effects. Due to the rapid hydrolysis of DPMA to DPM, DPMA

## Virbac SEBAZOLE Keratolytic, Keratoplastic, Antibacterial, Antifungal & Antipruritic Wash for Dogs & Cats

	<p>would not be expected to show teratogenic effects. At high doses where maternal toxicity occurs (e.g., significant body weight loss), an increased incidence of some anomalies such as delayed skeletal ossification or increased 13th ribs, have been reported. Commercially available PGEs showed no teratogenicity.</p> <p>The weight of the evidence indicates that propylene glycol ethers are not likely to be genotoxic. <i>In vitro</i>, negative results have been seen in a number of assays for PnB, DPnB, DPMA and TPM. Positive results were only seen in 3 out of 5 chromosome aberration assays in mammalian cells with DPnB. However, negative results were seen in a mouse micronucleus assay with DPnB and PM. Thus, there is no evidence to suggest these PGEs would be genotoxic <i>in vivo</i>. In a 2-year bioassay on PM, there were no statistically significant increases in tumors in rats and mice.</p>
<b>SODIUM THIOSULFATE &amp; SODIUM SALICYLATE &amp; SODIUM LAURYL SULFATE &amp; COCONUT DIETHANOLAMIDE &amp; PROPYLENE GLYCOL PHENYL ETHER</b>	<p>Asthma-like symptoms may continue for months or even years after exposure to the material ceases. This may be due to a non-allergenic condition known as reactive airways dysfunction syndrome (RADS) which can occur following exposure to high levels of highly irritating compound. Key criteria for the diagnosis of RADS include the absence of preceding respiratory disease, in a non-atopic individual, with abrupt onset of persistent asthma-like symptoms within minutes to hours of a documented exposure to the irritant. A reversible airflow pattern, on spirometry, with the presence of moderate to severe bronchial hyperreactivity on methacholine challenge testing and the lack of minimal lymphocytic inflammation, without eosinophilia, have also been included in the criteria for diagnosis of RADS. RADS (or asthma) following an irritating inhalation is an infrequent disorder with rates related to the concentration of and duration of exposure to the irritating substance. Industrial bronchitis, on the other hand, is a disorder that occurs as result of exposure due to high concentrations of irritating substance (often particulate in nature) and is completely reversible after exposure ceases. The disorder is characterised by dyspnea, cough and mucus production.</p>
<b>SODIUM SALICYLATE &amp; ECONAZOLE NITRATE</b>	<p>Exposure to the material for prolonged periods may cause physical defects in the developing embryo (teratogenesis).</p>
<b>4-CHLORO-3,5-XYLENOL &amp; ECONAZOLE NITRATE</b>	<p>The following information refers to contact allergens as a group and may not be specific to this product. 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>
<b>4-CHLORO-3,5-XYLENOL &amp; COCONUT DIETHANOLAMIDE</b>	<p>The material may produce moderate eye irritation leading to inflammation. Repeated or prolonged exposure to irritants may produce conjunctivitis.</p>

<b>Acute Toxicity</b>	✓	<b>Carcinogenicity</b>	⊖
<b>Skin Irritation/Corrosion</b>	✓	<b>Reproductivity</b>	⊖
<b>Serious Eye Damage/Irritation</b>	✓	<b>STOT - Single Exposure</b>	✓
<b>Respiratory or Skin sensitisation</b>	⊖	<b>STOT - Repeated Exposure</b>	⊖
<b>Mutagenicity</b>	⊖	<b>Aspiration Hazard</b>	⊖

**Legend:** ✗ – Data available but does not fill the criteria for classification  
 ✓ – Data required to make classification available  
 ⊖ – Data Not Available to make classification

## SECTION 12 ECOLOGICAL INFORMATION

### Toxicity

Ingredient	Endpoint	Test Duration (hr)	Species	Value	Source
sodium thiosulfate	LC50	96	Fish	16.88742mg/L	3
sodium thiosulfate	EC50	96	Algae or other aquatic plants	75416.391mg/L	3
sodium thiosulfate	EC50	384	Crustacea	1618.139mg/L	3
sodium thiosulfate	NOEC	0.08	Algae or other aquatic plants	50mg/L	4
sodium salicylate	LC50	96	Fish	144.354mg/L	3
sodium salicylate	EC50	96	Algae or other aquatic plants	420.600mg/L	3
sodium salicylate	EC0	24	Crustacea	80mg/L	4
sodium salicylate	NOEC	168	Algae or other aquatic plants	60mg/L	4
4-chloro-3,5-xyleneol	LC50	96	Fish	0.36mg/L	4
4-chloro-3,5-xyleneol	EC50	48	Crustacea	7.7mg/L	4
4-chloro-3,5-xyleneol	EC50	96	Algae or other aquatic plants	6.089mg/L	3

Continued...

## Virbac SEBAZOLE Keratolytic, Keratoplastic, Antibacterial, Antifungal & Antipruritic Wash for Dogs & Cats

econazole nitrate	EC50	96	Crustacea	400mg/L	5
sodium lauryl sulfate	LC50	96	Fish	0.59mg/L	4
sodium lauryl sulfate	EC50	48	Crustacea	0.67mg/L	4
sodium lauryl sulfate	EC50	96	Algae or other aquatic plants	1.2mg/L	4
sodium lauryl sulfate	BCF	1	Fish	0.85mg/L	4
sodium lauryl sulfate	EC50	96	Crustacea	0.12mg/L	4
sodium lauryl sulfate	NOEC	0.08	Fish	0.0000013mg/L	4
coconut diethanolamide	LC50	96	Fish	2.52mg/L	1
coconut diethanolamide	EC50	48	Crustacea	2.25mg/L	1
coconut diethanolamide	EC50	72	Algae or other aquatic plants	=2.2mg/L	1
coconut diethanolamide	EC0	96	Algae or other aquatic plants	1mg/L	1
coconut diethanolamide	NOEC	504	Crustacea	=0.07mg/L	1
propylene glycol phenyl ether	LC50	96	Fish	55.998mg/L	3
propylene glycol phenyl ether	EC50	96	Algae or other aquatic plants	194.345mg/L	3
propylene glycol phenyl ether	EC50	384	Crustacea	13.285mg/L	3
propylene glycol phenyl ether	LC50	96	Fish	57.916mg/L	3
propylene glycol phenyl ether	EC50	96	Algae or other aquatic plants	201.002mg/L	3
propylene glycol phenyl ether	EC50	384	Crustacea	13.740mg/L	3

**Legend:**

Extracted from 1. IUCLID Toxicity Data 2. Europe ECHA Registered Substances - Ecotoxicological Information - Aquatic Toxicity 3. EPIWIN Suite V3.12 - Aquatic Toxicity Data (Estimated) 4. US EPA, Ecotox database - Aquatic Toxicity Data 5. ECETOC Aquatic Hazard Assessment Data 6. NITE (Japan) - Bioconcentration Data 7. METI (Japan) - Bioconcentration Data 8. Vendor Data

**DO NOT discharge into sewer or waterways.**

Harmful to aquatic organisms, may cause long-term adverse effects in the aquatic environment.

**Persistence and degradability**

Ingredient	Persistence: Water/Soil	Persistence: Air
sodium thiosulfate	HIGH	HIGH
sodium salicylate	LOW	LOW
4-chloro-3,5-xyleneol	HIGH	HIGH
sodium lauryl sulfate	HIGH	HIGH
propylene glycol phenyl ether	LOW	LOW

**Bioaccumulative potential**

Ingredient	Bioaccumulation
sodium thiosulfate	LOW (LogKOW = -1.529)
sodium salicylate	LOW (LogKOW = 2.2447)
4-chloro-3,5-xyleneol	LOW (LogKOW = 3.27)
sodium lauryl sulfate	LOW (BCF = 7.15)
propylene glycol phenyl ether	LOW (LogKOW = 1.61)

**Mobility in soil**

Ingredient	Mobility
------------	----------

Continued...

## Virbac SEBAZOLE Keratolytic, Keratoplastic, Antibacterial, Antifungal & Antipruritic Wash for Dogs & Cats

sodium thiosulfate	LOW (KOC = 6.124)
sodium salicylate	LOW (KOC = 23.96)
4-chloro-3,5-xyleneol	LOW (KOC = 1186)
sodium lauryl sulfate	LOW (KOC = 10220)
propylene glycol phenyl ether	LOW (KOC = 18.74)

### SECTION 13 DISPOSAL CONSIDERATIONS

#### Waste treatment methods

<b>Product / Packaging disposal</b>	<ul style="list-style-type: none"> <li>▶ Containers may still present a chemical hazard/ danger when empty.</li> <li>▶ Return to supplier for reuse/ recycling if possible.</li> </ul> <p>Otherwise:</p> <ul style="list-style-type: none"> <li>▶ 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.</li> <li>▶ Where possible retain label warnings and SDS and observe all notices pertaining to the product.</li> </ul> <p>Legislation addressing waste disposal requirements may differ by country, state and/ or territory. Each user must refer to laws operating in their area. In some areas, certain wastes must be tracked.</p> <p>A Hierarchy of Controls seems to be common - the user should investigate:</p> <ul style="list-style-type: none"> <li>▶ Reduction</li> <li>▶ Reuse</li> <li>▶ Recycling</li> <li>▶ Disposal (if all else fails)</li> </ul> <p>This material may be recycled if unused, or if it has not been contaminated so as to make it unsuitable for its intended use. If it has been contaminated, it may be possible to reclaim the product by filtration, distillation or some other means. Shelf life considerations should also be applied in making decisions of this type. Note that properties of a material may change in use, and recycling or reuse may not always be appropriate.</p> <ul style="list-style-type: none"> <li>▶ <b>DO NOT allow wash water from cleaning or process equipment to enter drains.</b></li> <li>▶ It may be necessary to collect all wash water for treatment before disposal.</li> <li>▶ In all cases disposal to sewer may be subject to local laws and regulations and these should be considered first.</li> <li>▶ Where in doubt contact the responsible authority.</li> <li>▶ Recycle wherever possible.</li> <li>▶ 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.</li> <li>▶ Dispose of by: burial in a land-fill specifically licenced to accept chemical and / or pharmaceutical wastes or incineration in a licenced apparatus (after admixture with suitable combustible material).</li> <li>▶ Decontaminate empty containers. Observe all label safeguards until containers are cleaned and destroyed.</li> </ul>
-------------------------------------	--

### SECTION 14 TRANSPORT INFORMATION

#### Labels Required

<b>Marine Pollutant</b>	NO
<b>HAZCHEM</b>	Not Applicable

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

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

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

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

Not Applicable

### SECTION 15 REGULATORY INFORMATION

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

**SODIUM THIOSULFATE(7772-98-7) IS FOUND ON THE FOLLOWING REGULATORY LISTS**

Australia Inventory of Chemical Substances (AICS)

**SODIUM SALICYLATE(54-21-7) IS FOUND ON THE FOLLOWING REGULATORY LISTS**

Australia Hazardous Substances Information System - Consolidated Lists

Australia Inventory of Chemical Substances (AICS)

## Virbac SEBAZOLE Keratolytic, Keratoplastic, Antibacterial, Antifungal & Antipruritic Wash for Dogs & Cats

### 4-CHLORO-3,5-XYLENOL(88-04-0) IS FOUND ON THE FOLLOWING REGULATORY LISTS

Australia Hazardous Substances Information System - Consolidated Lists      Australia Inventory of Chemical Substances (AICS)

### ECONAZOLE NITRATE(24169-02-6) IS FOUND ON THE FOLLOWING REGULATORY LISTS

Australia Hazardous Substances Information System - Consolidated Lists      Australia Inventory of Chemical Substances (AICS)

### SODIUM LAURYL SULFATE(151-21-3) IS FOUND ON THE FOLLOWING REGULATORY LISTS

Australia Hazardous Substances Information System - Consolidated Lists      Australia Inventory of Chemical Substances (AICS)

### COCONUT DIETHANOLAMIDE(68603-42-9) IS FOUND ON THE FOLLOWING REGULATORY LISTS

Australia Inventory of Chemical Substances (AICS)      International Agency for Research on Cancer (IARC) - Agents Classified by the IARC Monographs

### PROPYLENE GLYCOL PHENYL ETHER(41593-38-8) IS FOUND ON THE FOLLOWING REGULATORY LISTS

Australia Inventory of Chemical Substances (AICS)

National Inventory	Status
Australia - AICS	Y
Canada - DSL	Y
Canada - NDSL	N (coconut diethanolamide; sodium thiosulfate; sodium lauryl sulfate; 4-chloro-3,5-xyleneol; econazole nitrate; propylene glycol phenyl ether; sodium salicylate)
China - IECSC	N (econazole nitrate)
Europe - EINEC / ELINCS / NLP	Y
Japan - ENCS	N (econazole nitrate)
Korea - KECI	Y
New Zealand - NZIoC	Y
Philippines - PICCS	N (econazole nitrate)
USA - TSCA	N (econazole nitrate)
<b>Legend:</b>	Y = All ingredients are on the inventory N = Not determined or one or more ingredients are not on the inventory and are not exempt from listing(see specific ingredients in brackets)

## SECTION 16 OTHER INFORMATION

### Other information

#### Ingredients with multiple cas numbers

Name	CAS No
sodium thiosulfate	7772-98-7, 10102-17-7
4-chloro-3,5-xyleneol	88-04-0, 1321-23-9
econazole nitrate	24169-02-6, 68797-31-9
sodium lauryl sulfate	151-21-3, 1335-72-4, 3088-31-1, 9004-82-4
coconut diethanolamide	68603-42-9, 61791-31-9, 71786-60-2, 8036-48-4, 8040-31-1, 8040-33-3, 12751-06-3, 53028-62-9, 56448-72-7, 56832-66-7, 63091-31-6, 66984-58-5, 67785-10-8, 67785-14-2, 71343-51-6, 71343-71-0, 83652-14-6, 87714-18-9, 90651-47-1, 118104-13-5, 153189-69-6, 186615-78-1
propylene glycol phenyl ether	41593-38-8, 770-35-4, 4169-04-4

Classification of the preparation and its individual components has drawn on official and authoritative sources as well as independent review by the Chemwatch Classification committee using available literature references.

A list of reference resources used to assist the committee may be found at:

[www.chemwatch.net](http://www.chemwatch.net)

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

### Definitions and abbreviations

PC—TWA: Permissible Concentration-Time Weighted Average

PC—STEL: Permissible Concentration-Short Term Exposure Limit

IARC: International Agency for Research on Cancer

Continued...

**Virbac SEBAZOLE Keratolytic, Keratoplastic, Antibacterial, Antifungal & Antipruritic Wash for Dogs & Cats**

ACGIH: American Conference of Governmental Industrial Hygienists

STEL: Short Term Exposure Limit

TEEL: Temporary Emergency Exposure Limit.

IDLH: Immediately Dangerous to Life or Health Concentrations

OSF: Odour Safety Factor

NOAEL :No Observed Adverse Effect Level

LOAEL: Lowest Observed Adverse Effect Level

TLV: Threshold Limit Value

LOD: Limit Of Detection

OTV: Odour Threshold Value

BCF: BioConcentration Factors

BEI: Biological Exposure Index

This document is copyright.

Apart from any fair dealing for the purposes of private study, research, review or criticism, as permitted under the Copyright Act, no part may be reproduced by any process without written permission from CHEMWATCH.

TEL (+61 3) 9572 4700.