Toxicology & Regulatory Affairs
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Toxicological Risk Assessment

Product:	Therma-kool gel pads (Nortech)
Limitation	Assessment of gel only
Prepared for:	Intertek
New or Revision:	New
Date of Issue	04 November, 2009

Introduction

Nortech, through Intertek, requested a toxicology review of the gel used in Nortech's Therma-kool gel pads. The pads are medical devices consisting of a sealed flexible plastic bag filled with gel. The gel-packs are co-marketed with blue non-woven sleeves or sleeves made to fit over a shoulder or other locations on the body. Sales literature indicated the bags may be placed in the freezer before use for a cooling effect or in a microwave oven for a warming effect. This toxicology review is limited to the potential hazards of the gel filling should it leak out or be otherwise removed. No consideration is given to the plastic bag's composition (polymers, stabilizers, antioxidants or plasticizers) or the non-woven sleeve.

Documentation

Information received for review (Email as pdf file)

- Formulation sheet
- Polymer COA
- Preservative COA (Mallinckrodt)
- Glycerin COA (Oleon)
- MSDS Therma-Kool Compress
- Answers to specific questions
    - There are no colorants or fragrances used in this formulation.
    - Gel pH between 5-8.
    - There are no complaints that have been received from consumers

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Description

The gel is a water solution of glycerin and polymer that is neutralized with sodium hydroxide and preserved with a bactericide..

Exposures

For the purpose of assessment, the following assumptions were made, these are strictly assumptions made without knowledge of actual exposures:

- No exposure occurs with normal use as the gel is sealed in a rugged plastic bag.
- Dermal exposure could occur if the gel leaked from a bag. For example a person resting with a gel pad might fall asleep and roll on to the pad. If the bag had been damaged previously, 100 ml would leak out and saturate the sleeve and clothing without waking the user and the exposure could last of 4 hours.
- Oral Exposure: Oral exposure may occur by transfer from hand to mouth of a few grams gel. A child might encounter a bag with a small lead and suck out 25 ml gel. Since glycerin is somewhat sweet they might continue to swallow significant amounts of gel.

Sources of information.

Literature searches of individual components using Toxline and PubMed are conducted on each component in addition to internet searches for commercial information and to locate MSD sheets. Highbeam data base is used to search trade publications. Standard textbooks in toxicology and clinical toxicology and a wide variety of handbooks and encyclopedic references are available at TRA. STN may also be searched as well as numerous standard chemistry resources.

Method of Assessment

Unless data are available concerning the entire formulation, or the interaction of two or more components of the formulation, each component is first considered independently and secondly in context of exposure to other components if there is any confidence that joint effects might occur.

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Composition

The following components and percentage in the formulation were supplied:

			Availably and strength of health effects data		Regulatory Issues for US or EU	Level of concern
	CASNO	Percent	Human	Lab Animals		
Water			NA	NA	None Identified	None
Glycerin	56-81-5		Good	Good	None Identified	Low
Polymer			Fair	Good	None Identified	Very Low
Preservative			Good	Good	None Identified	Low
Sodium hydroxide	1310-73-2		NA	NA	None Identified	Very Low

Assessment of Individual Components

Glycerin

Glycerin from natural vegetable sources is used in the gel. Presumably, it is used to lower the freezing point of the water and interfere with crystalline ice formation. With a molecular weight of 92, this solution is predicted to lower the freezing point of water by about 3 C. This is a fairly modest reduction as compared to solutions of ethanol but it is well suited to this device which is designed to have indirect contact with skin with a layer of non-woven fabric between the device and exposed skin. Direct skin contact is considered a foreseeable misuse and should be considered. Provided there is mixture of liquid phase and solid phase (ice) in the chilled bag the temperature of the gel is expected to remain at about -2 to -4 C. This temperature would prevent significant damage to the skin by freezing while providing a high degree of cooling.

Toxicity of glycerin is expected to be low as it is found in many foods end is a normal metabolic substance in humans. It is a well studied material and its specific function in the body is well understood and, as far as is known, it has no specific pharmacological activity. Never the less, it is used as an FDA approved diuretic because of its osmotic properties and lack of other activity. As a diuretic drug substance it is orally active. The half life of glycerin in the blood is very short and in the range of 20 to 50 minutes with metabolism by normal physiologic pathways accounting for most of the loss and the remainder excreted

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unchanged by the kidneys. It's mechanism of action is to extract water from intracellular compartments and inhibit resorption of water and electrolytes by the kidneys. This can potentially lead to imbalance of serum electrolytes resulting in headache, nausea and vomiting. Glycerin can also be converted to glucose which could result in hyperglycemia.

Oral Toxicity: The adult therapeutic dose is 1-2 grams/kg body weight and for children the therapeutic dose is 1-1.5 g/kg. Prescribing information notes that no unusual adverse or side effects are anticipated in children; however, this has not been thoroughly investigated. Reported adverse effects are headache, nausea and vomiting, with less common side effects of diarrhea and dizziness. Rare side effects are irregular heartbeat and confusion, presumably resulting from electrolyte imbalance. A recent publication (Clin Toxicol (Phila). 2009 Apr;47(4):312-6)describes severe intoxication in an adult who received an accidental oral overdose (calculated to be approximately 3.9 g/kg) and apparently recovered.

Glycerin is also administered to adults and children rectally in suppositories to relieve constipation. Based on the recommended diuretic dose for adults of 1-2 g/kg and children of 1 to 1.5 g/kg, the lower end of the range (1 g/kg) would be a dose of 70 g for a 70 kg adult and 15 g for a 15 kg child. These numbers must be used with caution when considering oral dosing as glycerin is reportedly not well adsorbed after rectal administration. Relatively large oral doses have produced intoxication, heamolysis and acute renal failure and are potentially fatal. The Lowest Lethal Dose for humans was reported as 1428 mg/kg (SIDS Document 2002 from 1969 anonymous source).

Using the reported lowest LD_{50} of 1428 mg/kg and converting it into gel volume, a 8 kg child would require oral consumption of >50 ml of glycerol gel to achieve the 1428 mg/kg lowest reported LD_{50}. Although this LD_{lo} is not considered highly reliable, it is published in various sources and cannot be categorically rejected without additional information. As a worst case example a 8 kg child in a crib with a leaking bag of gel could dermally absorb a few grams of glycerin from saturated bedding and if the leak was in a bag's corner such that the child could suck fluid from the bag, it could happen that 50 or more ml of gel were orally consumed, blood glycerol levels could reach a dangerous level. Admittedly, this set of circumstances would probably never occur but it puts some perspective on the possible toxicity of glycerin to a small child.

Assessing potential health effects from dermal exposure, it is noted that glycerin is contained in many soaps and skin lotion preparations available to the public. As glycerin is a neutral molecule of relatively low molecular weight some dermal absorption is expected but achieving toxic levels by only dermal exposure has never been reported.

Conclusion for Glycerin.

Oral or dermal exposure to glycerin is not an intended event for this material. In the event that a bag breaks or is punctured, oral or dermal exposure could occur but it would likely be a one-time event. Since glycerin is readily metabolized and is of low toxicity the probability of a consumer suffering a toxic or intoxicating overdose of glycerin is negligible but cannot be categorically excluded from consideration.

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Polymer.

This component is a member of a family of high molecular weight polymers that are not absorbed orally or dermally. Oral consumption of this polymer could result in gastrointestinal irritation leading to vomiting and diaherra.

Mild eye irritation cannot be excluded if eye contact should occur and although the pure polymer is listed as a potential skin irritant on it's MSDS, the dilute solution used is not expected to cause any skin irritation or sensitization.

This family of polymers has caused adverse effects in experimental animals after exposure by inhalation. With this material, inhalation exposure would require aerosolization and there are no circumstance in the use of these pads that would result in aerosol exposure of consumers.

Conclusion :

No concern for use at this level in gel-packs

Preservative:

Descripton: A small molecule that is proven to be effective. They are widely used as preservatives in cosmetics, toiletries, and pharmaceuticals due to their relatively low toxicity profile and a long history of safe use. Based on acute, subacute and chronic toxicity studies in rats, dogs and mice, this preservative has been shown to be practically non-toxic, not carcinogenic, not genotoxic nor co-carcinogenic, and not teratogenic. A NOAEL for general toxicity of 1000 mg/kg bw/day has been determined for this material Likewise, it is not a skin irritant and is only a mild to moderate eye irritants. It is not skin a sensitizers on intact skin but has shown some sensitization potential on broken or abraded skin.

They have received quite a bit of attention in the last few years related to their estrogenic potential and subsequent potential for developmental toxicity. Testing has revealed to varying degrees that individual materials have weakly estrogenic activity in some in vitro screening tests. The estrogenic potency is still 1000 to 1,000,000 times below the potency of 17β-estradiol. Testing in vivo has proven negative.

The EU Scientific Committee on Consumer Products (SCCP) has recently issued an opinion of safety for this material. The US FDA has reaffirmed their position on the safety of this material in a position paper updated in 2007.

Regulatory limitations for various applications are in place in the EU and the usage here is well below limits.

Although the estrogenicity issue had not disappeared, the regulatory authorities have taken a firm stand that the *in vitro* estrogenicity has no relationship to adverse effects on human health when it is used as recommended. It is unlikely that any sort of ban will be enacted but eventually the allowable limits may be lowered which should not affect this product.

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Conclusion for Preservative

In spite of recent controversy concerning estrogenicity the scientific evidence supports a high degree of safety for the consumer at this concentration in the product.

Sodium Hydroxide

This material is simply used to adjust the pH. There is no concern over its use in the product

Conclusions and Recommendations:

Based on the information provided this material (gel) does not pose a threat to the consumer when used under normal and reasonably foreseeable conditions of use and is considered regulatory compliant with the laws and regulations in the US and the EU.

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