File No: NA/19

NATIONAL INDUSTRIAL CHEMICALS NOTIFICATION AND ASSESSMENT SCHEME

FULL PUBLIC REPORT

ISOLUTROL

Under subsection 38(5) of the Industrial Chemicals (Notification and Assessment) Act 1989 (the Act), the Director of Chemicals Notification and Assessment publishes this Full Public Report by giving a copy of it to each member of the National Occupational Health and Safety Commission.

For the purposes of subsection 78(1) of the Act, copies of this Full Public Report may be inspected by the public at:

The Library
Worksafe Australia
92-94 Parramatta Road
Camperdown NSW 2050

between the hours of 10.00 am and 12 noon and 2.00 pm and 4.00 pm each week day except on public holidays.

Director
Chemicals Notification and Assessment

Date:

FULL PUBLIC REPORT

ISOLUTROL

1. IMPORTER/ MANUFACTURER

McFarlane Marketing (Australia) Pty. Ltd., 7 Hall Street, Hawthorn East, Victoria 3123.

2. IDENTITY OF THE CHEMICAL

Trade name: Isolutrol

3. PHYSICAL AND CHEMICAL PROPERTIES

At room temperature and atmospheric pressure, Isolutrol is a white amorphous powder of negligible volatility and a very slight amine odour. Its physical and chemical properties include:

Melting point:	171-173^{o}C
Density:	989 kg/m^{3}
Water solubility:	200 g/L (@ 20^{o}C ± 0.5^{o}C)
Hydrolysis:	< 10% hydrolysed after 5 days (@ 50^{o}C ± 0.1^{o}C, pH = 4.0, 7.0, 9.0). $t_{1/2}$ > 1 year
Partition coefficient:	$P_{o/w}$ = 0.0135 (@ 23^{o}C)
Dissociation constant:	K_a = 1.12 x 10^{-7} moles/L (@ 20^{o}C)
Flammability:	non-flammable

Reactivity:	stable at room temperature; heat (@ 47^{o}C $\pm$ 0.1^{o}C) and ultraviolet irradiation results show < 10% reactivity in 6 days. $t_{1/2}$ > 1 year.

4. METHODS OF DETECTION AND DETERMINATION

Infrared spectroscopy and Nuclear Magnetic Resonance spectroscopy are used for structural elucidation of Isolutrol.

High Pressure Liquid Chromatography is used for determining the purity of Isolutrol.

5. PURITY OF THE CHEMICAL

Degree of purity: > 99% w/w

Non-hazardous impurities: inorganic salts (0.2% w/w)

6. INDUSTRIAL USE

Isolutrol is an extract of shark bile and it is to be used exclusively as an excipient in cosmetics. It is estimated that in any one year, 1 kg of Isolutrol will be formulated locally into cosmetic products, the remainder will be exported.

7. OCCUPATIONAL EXPOSURE

Raw dried shark bile, a granular powder, will be imported in sealed polyethylene bags. Therefore, occupational exposure during transit is unlikely except in the event of an accidental spillage. The same applies to its extract, Isolutrol, which will be stored and transported in sealed polyethylene packages to approved customers.

In the factory environment, the receipt and handling of raw shark bile and the production and packaging of its extract, Isolutrol, will be performed by two operators. These workers may be exposed

to Isolutrol solution when it is manually transferred from the drums to the rotary vacuum evaporator and when the concentrate is transferred into flasks for freeze drying. Exposure to dried Isolutrol may take place when it is manually ground in a mortar, during packaging and purity analysis. It is anticipated that occupational exposure to Isolutrol will be low due to the small amount (< 200 g) manufactured in any one operating day; its physical properties characterised by high water solubility and negligible vapour pressure; and the use of personal protection equipment such as safety glasses, protective clothing and if necessary disposable dust masks.

The main occupational hazard during the manufacture of Isolutrol is the exposure to the solvent, methanol. If control and personal protection procedures are not implemented, exposure to this solvent can be high.

Isolutrol will be incorporated into cosmetic formulations as an excipient. Therefore, it is possible for workers involved with the manufacture of these cosmetic products to be exposed to Isolutrol. An assessment of the occupational exposure to Isolutrol when used in this manner is presently not possible because no data is available as the marketing of this chemical to the cosmetic industry has yet to take place.

8. PUBLIC EXPOSURE

Public exposure to Isolutrol would occur since it is to be used as an excipient in cosmetics. At present, information on the type of cosmetics for sale in Australia which would include Isolutrol is unavailable as the marketing of this chemical to the Australian cosmetic industry has yet to take place. Therefore, the extent of public exposure to this chemical when used in cosmetic formulations is unclear.

9. ENVIRONMENTAL EXPOSURE

Release

The manufacturing process of Isolutrol suggests that release to the environment from the manufacturing site will be minimal. Wastes from the extraction process, particularly

methanol, spills, spoilage etc will be disposed in approved landfill sites.

The use of Isolutrol as an excipient in cosmetics will result in near total release to the environment.

Fate

Virtually all of the chemical after formulation into cosmetics will be discharged to the sewerage.

The notifier states that Isolutrol will be formulated into cosmetics at a very low concentration and that 100,000 x 100 mL cosmetic units would enter the Australian market. No information was provided on the type of cosmetics which is likely to include Isolutrol. Assuming that the cosmetic is for facial application and 5 mL of the cosmetic is applied all of which is ultimately washed off with water (shower - 50 litres), the concentration of Isolutrol entering the sewerage system would be in the tens of ppb. Assuming that a 100 fold dilution occurs in the sewerage system and a further 100 fold dilution in the sewerage treatment plant, the resulting discharge into receiving waters will have an Isolutrol concentration of about 1 part per trillion, as a worst case.

The cosmetic container and residual lotion will be released to domestic waste stream into an approved landfill site. The quantity of Isolutrol disposed in this manner is likely to be insignificant in the overall quantity of domestic waste.

No biological degradation data are available but are not required at this level. The hydrolytic, heat and UV light stability tests indicated that the chemical has a half-life greater than 1 year.

10. ASSESSMENT OF TOXICOLOGY DATA

10.1 Acute Toxicity Studies

Table 1 Summary of acute toxicity of Isolutrol

Test	Species	Outcome	Ref.
Oral	CD Rats	LD_{50}: > 5000 mg/kg	1
CFLP	(ICI Strain) mice	LD_{50}:> 5000 mg/kg	2
Intravenous	CD Rats	LD_{50}: males 149 mg/kg females 147 mg/kg	3
	CFLP (ICI Strain 1) mice	LD_{50}: males 337 mg/kg females 310 mg/kg	4
Dermal irritation	NZ white rabbits	non-irritant	5
Eye irritation	NZ white albino rabbits	non irritant	6

10.1.1a Acute Oral Toxicity in Rats (1)

This study was performed according to the OECD Guidelines for Testing of Chemicals No: 401 (1981) (7).

In a range-finding study, single doses of 1000 and 2500 mg/kg bodyweight of Isolutrol in distilled water were administered by gavage to two groups of two male and two female CD rats. These animals were observed for five days. No deaths were noted during the study period. Results from this test indicate an oral LD_{50} > 2500 mg/kg bodyweight for Isolutrol.

In the main study, a single dose of 5000 mg/kg bodyweight of Isolutrol in distilled water was administered by gavage to five male and five female CD rats. The animals were observed for 14 days. Pilo-erection, abnormal body carriage, abnormal gait,

lethargy, decreased respiratory rate, ptosis and diarrhoea were observed in all animals. Two deaths were noted on Day 2 of the study. In all surviving animals, recovery was complete by Day 3. Gain in bodyweight was not affected by treatment. Necropsy on all animals, including those which died during the study, revealed no macroscopic abnormalities. Results from this study indicate an oral LD_{50} > 5000 mg/kg bodyweight of Isolutrol in rats.

10.1.1b Acute Oral Toxicity in Mice (2)

This study was performed according to the OECD Guidelines for Testing Chemicals No: 401 (1981) (7).

A single dose of 5000 mg/kg bodyweight of Isolutrol was administered by gavage to five male and five female CFLP (ICI Strain 1) mice. These animals were observed for 14 days. No deaths were noted during the study period. Pilo-erection, pallor of the extremities and diarrhoea were observed in all animals. Recovery was complete by Day 2 of the study. Gain in bodyweight was unaffected by treatment. Necropsy on all animals revealed no macroscopic abnormalities. Results from this study indicate an oral LD_{50} > 5000 mg/kg bodyweight of Isolutrol in mice.

10.1.2a Acute Intravenous Toxicity in Rats (3)

In a range-finding study, single doses of 100 and 160 mg/kg bodyweight of Isolutrol in water for injection were each administered intravenously to groups of two male and two female CD rats. A single dose of 2500 mg/kg bodyweight was administered intravenously to one male and one female rat. These animals were observed for five days. No deaths were recorded in the 100 mg/kg dose group. All animals in the 160 and 2500 mg/kg dose groups died within 15 minutes following treatment. Results from this study indicate that the intravenous LD_{50} for Isolutrol in both male and female rats is between 100 and 160 mg/kg bodyweight.

In the main study, single doses of 100, 126 and 160 mg/kg bodyweight of Isolutrol in water were each administered intravenously to groups of five male and five female CD rats. These animals were observed for 14 days. Pilo-erection, decreased respiratory rate, pallor of extremities and arching were noted at all dose levels. Abnormal body gait and lethargy were noted at dose levels of 126 mg/kg and above. Abnormal body

carriage was observed at 160 mg/kg. In surviving animals, recovery was complete by Day 3. Deaths were noted amongst males dosed at 126 mg/kg (2/5) and 160 mg/kg (3/5), and amongst females dosed at 100 mg/kg (1/5), 126 mg/kg (1/5) and 160 mg/kg (3/5). Death occurred from within 15 minutes to one hour following dosing. No change in bodyweight was recorded for rats that died and necropsy revealed no macroscopic abnormalities. Necropsy on surviving animals revealed no abnormal macroscopic findings. Results from this study indicate an intravenous LD_{50} of 149 mg/kg bodyweight of Isolutrol in male rats and 147 mg/kg in female rats.

10.1.2b <u>Acute Intravenous Toxicity in Mice (4)</u>

In a range-finding study, single doses of 250 and 640 mg/kg bodyweight Isolutrol in water for injection were each administered intravenously to groups of two male and two female CFLP (ICI Strain 1) mice. These animals were observed for five days. Deaths were noted in one female dosed at 250 mg/kg, and in all animals at the higher dose of 640 mg/kg. Death occured within 15 minutes of dosing. Results from this study indicate that the intravenous LD_{50} of Isolutrol in male mice is between 250 and 640 mg/kg bodyweight, and in female mice, 250 mg/kg bodyweight.

In the main study, single doses of 200, 320 and 500 mg/kg bodyweight of Isolutrol in water for injection were each administered intravenously to groups of five male and five female CFLP (ICI Strain 1) mice. These animals were observed for 14 days. No deaths were recorded at 200 mg/kg, but deaths were noted at 320 mg/kg (2/5 males; 2/5 females) and at 500 mg/kg (5/5 males; 5/5 females). Death occured within 15 minutes of dosing. Clonic convulsions were observed within five minutes of dosing, immediately prior to death in all animals dosed at 500 mg/kg. Other reactions observed in the lower dose groups were pilo-erection, abnormal body carriage, decreased respiratory rate, ptosis, pallor of extremities, abnormal gait and discolouration of the injection site, but recovery was complete by Day 3. Results of this study indicate an intravenous LD_{50} of 337 mg/kg bodyweight of Isolutrol in male mice and 310 mg/kg in female mice.

10.1.3 Acute Dermal Irritation/ Corrosion (5)

This study was performed according to the OECD Guidelines for Testing Chemicals No: 404 (1981) (8).

A single dose of 0.5 ml of Isolutrol lotion (concentration 0.02% w/v) was administered to the clipped backs of each of three New Zealand White rabbits. Control sites were left untreated. The test substance was held in place with semi-occlusive material. The animals were exposed to the test substance for four hours. Dermal reactions were assessed according to Draize (9) 1, 24, 48 and 72 hours post-treatment. No dermal response was noted at the test and control sites of all animals during the 72 hours observation period. Results from this study indicate that Isolutrol is non-irritating to rabbit skin.

10.1.4 Acute Eye Irritation/ Corrosion (6)

This study was performed according to the OECD Guideline for Testing of Chemicals No: 405 (1987) (10). In addition to the specific observations required by the OECD, evaluations were made of pain responses at instillation; discharge from the eye; and the area of cornea affected by the lesions.

A single dose of 0.1 ml of Isolutrol lotion (concentration 0.02% w/v) was instilled into one eye of each of three New Zealand White rabbits; the other eye acting as control. Immediately following treatment, assessment of initial pain response was carried out according to the criteria stated in the study report (6). Instillation of the test substance was found not to have caused pain in any of the animals tested. Ocular reactions were assessed according to Draize (9) 1, 24, 48 and 72 hours post-treatment. No ocular reactions were observed in the controls. Redness of the conjunctiva was observed in two animals 24 and 48 hours post-treatment however, by 72 hours both animals had recovered. The mean values of these reactions indicate that Isolutrol is not an eye irritant in rabbits.

10.2 Repeated Dermal Application (11)

Two groups of six New Zealand White rabbits were used in this study. Two ml of Isolutrol lotion (0.02% w/v) was applied to the clipped right flange of each rabbit in the test group, once a day, five days a week for six consecutive weeks; the left flange was left untreated. The control group was also left untreated.

These animals were observed for seven weeks. Skin reactions were assessed according to Draize (9). Skin fold thickness was also recorded. No skin reactions were observed at the untreated sites of test animals or in the control group of animals. Small lesions were observed in two test animals on Day 12 but these effects were transient. One of these animals developed an abcess which was completely resolved by Day 30. The daily index scores for erythema and oedema were zero in all the test and control animals. No deaths were noted and no adverse clinical signs were observed. Gain in bodyweight and skin fold thickness were unaffected. Necropsy revealed no abnormal macroscopic findings. Results from this study indicate that repeated applications of Isolutrol is non-irritating to rabbit skin.

10.3 Delayed Contact Hypersensitivity (12)

This study was performed according to the OECD Guideline for Testing Chemicals No: 406 (1981) (13). The test procedure employed was the Guinea Pig Maximisation Test (14).

Thirty female Hartley/ Dunkin strain albino guinea-pigs (20 test animals and 10 control animals) were used in this study. At separate sites, the test animals were induced with intradermal injections of 0.02% w/v of Isolutrol lotion and a 50% v/v solution of Isolutrol in Freund's complete adjuvant, followed by the topical application of Isolutrol lotion one week later. Controls were similarly treated but with the omission of the test substance. Two weeks after the induction, the test and control animals were challenged topically with a 50% v/v aqueous solution of Isolutrol. The challenge sites were evaluated 24, 48 and 72 hours post-treatment. Dermal responses were assessed according to Draize (9). No dermal reactions were observed in any of the test or control animals. Gain in bodyweight was unaffected. Results from this study indicate that Isolutrol lotion at a concentration of 0.02% w/v does not produce delayed contact hypersensitivity in guinea-pigs.

10.4 Salmonella typhimurium Reverse Mutation Assay (15)

This study was performed according to the OECD Guideline for Testing Chemicals No: 471 (1983) (16).

In a range-finding study, Isolutrol, at dose levels of 5, 50, 500 and 5000 µg/plate, was tested for gene mutation according to the Ames procedure using *Salmonella typhimurium* strains TA 1535, TA

1537, TA 1538, TA 98, TA 100, in both the presence and absence of metabolic activation. The solvent, water, was used as the negative control. No increase in revertant colony numbers of any significance was observed in any of the strains exposed to the test substance, both in the presence and absence of metabolic activation. Isolutrol was thus found to be non genotoxic towards the tester strains at the dose levels tested.

In the main study, Isolutrol, at dose levels of 0, 50, 150, 500, 1500 and 5000 ug/plate, was tested in the presence and absence of metabolic activation. This test was repeated. The solvent, water, was used as the negative control. Positive controls used were N-ethyl-N'-nitro-N-nitrosoguanidine, 9-aminoacridine, 2-aminoanthracene and 2-nitrofluorene.
No increase in revertant colony numbers of any significance was observed in any of the strains exposed to the test substance, both in the presence and absence of metabolic activation. Isolutrol was thus found to be non-mutagenic to the test strains at the dose levels tested.

10.5 <u>An androgenic study of Isolutrol (17)</u>

20 *White Male Wistar* rats were castrated and were divided randomly into five groups. One group was used as the control and the remaining four groups were each subcutaneously injected for seven days with testosterone propionate in incomplete Freund's adjuvant (10 mg/day); Isolutrol in incomplete Freund's adjuvant at concentrations of 0.014 mg/day; 0.14 mg/day and 14 mg/day, respectively. Also included as control was a sixth group which consisted of four rats which were left whole and untreated. No significant alteration in weight of the seminal vesicles was observed in the Isolutrol treated animals when compared to untreated castrates and untreated whole animals. However, the castrated animals treated with testosterone experienced a significant increase in weight of the seminal vesicles. No significant change in weight of the levator ani muscles was observed in the Isolutrol treated animals when compared to untreated castrates and untreated whole animals. However, in the testosterone treated animals the weight of the levator ani muscles was markedly increased. The results of this study indicate that at the dose levels used in this study, Isolutrol does not exhibit androgenic or myotrophic effects.

10.6 Overall Assessment of Toxicology Data

Isolutrol has very low acute oral toxicity (oral LD_{50} in rats: > 5000 mg/kg; oral LD_{50} in mice: > 5000 mg/kg). The intravenous LD_{50} of Isolutrol in male rats is 149 mg/kg; in female rats 147 mg/kg; in male mice 337 mg/kg and in female mice 310 mg/kg. The lower LD_{50} values by intravenous administration are consistent with the ionic nature of the chemical as only non-ionised moeities which are usually lipid-soluble can readily penetrate cell membranes thus facilitating absorption of the chemical from the gut (18). Tests on rabbits have revealed that at a concentration of 0.02% w/v Isolutrol is not an eye or skin irritant and prolonged dermal application is not likely to result in any irritation. Other tests have shown that Isolutrol is unlikely to be androgenic or myotrophic and that it exhibits low allergenic and mutagenic potential.

11. ASSESSMENT OF CLINICAL DATA

11.1 A double-blind randomised three stage rising dose Phase 1 study to determine the safety, irritation and allergenic potential of an aqueous solution of Isolutrol in healthy human volunteers (repeat insult patch test) (19)

63 healthy adult human volunteers, males and females, were recruited for this study. One subject withdrew from the study after the fourth application session because of anxiety about blood sampling.

Induction

During the three-week induction phase, 10 applications of an aqueous solution of Isolutrol (0.5 ml) were administered hypodermically to the back of each subject at concentrations of 0.1 mg/ml (22 subjects), 1.0 mg/ml (21 subjects) and 2.0 mg/ml (20 subjects). Placebo (0.5 ml normal saline) was applied to an adjacent site to the test site. One subject in the 1.0 mg/ml group withdrew after the fourth application. These sites were occluded until treatment was repeated at 48 hours and thereafter at 24 hour intervals. Skin reactions were assessed according to a scoring system (19). Slight erythema was observed at Isolutrol concentrations of 0.1 mg/ml (3/22), 1.0 mg/ml (3/21) and 2.0

mg/ml (1/20). These reactions were observed within three applications sessions. The effects were transient in all subjects. Slight erythema was observed at the placebo sites of 6/63 subjects. Four of these subjects showed similar and simultaneous response at both placebo and treatment sites. No other clinical signs of toxicity were observed. All subjects were rested for 13 days before being challenged.

Challenge

Isolutrol at a concentration of (1.0 mg/ml) and placebo were administered to all subjects as separate sites on either the forearm or the thigh. At 48 hours, skin reactions were assessed and the treatment was repeated. Skin reactions were again assessed 72 and 96 hours post the original treatment. No skin reactions were noted at any of the Isolutrol test sites. However, one subject experienced slight erythema/ irritation at the placebo site. No other clinical signs of toxicity were observed.

The results of this study indicate that Isolutrol is not a skin irritant nor a skin sensitiser at the dose levels used.

11.2 Human Photosensitization Test (20)

The photosensitisation potential of Isolutrol in human volunteers was studied by means of a repeated patch application procedure (21).

10 female volunteers (25-54 years of age) were recruited for this study.

Pretreatment - The Minimal Erythema Dose (MED) Assessment

The MED is the lowest dose of ultraviolet (UV) radiation which elicits significant erythema at a test site. Prior to the start of treatment, the minimal erythema dose (MED) of ultraviolet (UV) radiation for unprotected skin of each subject was determined by exposing the area of the skin to be tested to ultraviolet (UV) radiation. The MED testing area was divided into five subsites and the exposure time for each subsite was 1.25 times greater than the previous site. After exposure, any immediate skin responses were scored (20).

Induction

Test patches containing three dics, two containing 0.4 ml 0.01% w/v aqueous Isolutrol and the third containing 0.4 ml distilled water, were applied to each subject's back (away from the MED sites) on Days 1, 4, 8, 11, 16 and 19 of the trial. The patches were held in place for 24 hours before being removed for UV exposure. One of the Isolutrol sites and the control distilled water site were irradiated with three times the subject's MED of UVA+B. The second Isolutrol site was not irradiated. After irradiation, all test sites were kept covered from sunlight for the duration of the test.

Challenge

On Day 29, the study was repeated using the same test sites and the same order of application of the test samples as used previously in the *Induction* phase. On Day 30, the two previously irradiated sites received 10 joules/ cm^2 of UVA. 24, 48 and 72 hours post irradiation, the skin was assessed for responses (20).

Isolutrol (0.01% w/v aqueous solution) showed no evidence of phototoxicity or photosensitisation in this group of ten human female subjects.

12. ASSESSMENT OF PUBLIC AND OCCUPATIONAL HEALTH AND SAFETY EFFECTS

Isolutrol has not yet been manufactured for use commercially therefore there is no data relating to the exposure of workers or the public to this chemical. As a result, there is no information on the effect of this chemical on human health. However, results from acute oral, dermal and ocular toxicity tests in animals indicate that Isolutrol is of low toxicity, even with repeated usage over short periods. There is no chronic toxicity data thus possible effects due to long term exposure are unknown. Clinical studies on human subjects show no skin irritation or sensitisation effects (19) or phototoxicity or photosensitisation effects (20). Androgenic effects were not observed in a study on rats (17). Because of its ionic nature, this chemical will not be readily absorbed across cell membranes (18). Therefore, no adverse health effects are anticipated during the handling and use of this chemical in the factory environment. The assessment of possible health hazard associated

with use of this chemical in cosmetic formulations must await notification of its exact use pattern.

The physical/ chemical properties of Isolutrol indicate that this chemical does not present any safety hazard to workers as it has very low volatility, is not flammable and is stable at room temperature.

The main occupational hazard in the factory environment is associated with exposure to the solvent, methanol. Overexposure to methanol may result in symptoms characterised by visual disturbances and metabolic acidosis (22). Methanol is highly flammable thus creating fire hazards when exposed to heat, flame or oxidisers. Moreover, methanol vapours are explosive when exposed to heat or flame. Therefore, the necessary precautions to be taken when handling hydrocarbon solvents such as methanol should be implemented. Engineering controls such as local exhaust ventilation should be employed to ensure that the workplace is well ventilated and worker exposure to methanol is maintained below the recommended exposure standard (TWA: 200 ppm) (23).

13. ASSESSMENT OF ENVIRONMENTAL EFFECTS

No toxicological studies of Isolutrol on aquatic organisms have been provided. This is acceptable for the proposed level of manufacture. Aquatic toxicity is not expected due to its high water solubility. Results from animal toxicology studies indicate that the chemical is practically non-toxic to terrestrial vertebrates.

14. ASSESSMENT OF ENVIRONMENTAL HAZARD

The predicted environmental concentration appears to be well below that which would be toxic to fauna. Despite the lack of toxicity data for aquatic organisms it seems unlikely that Isolutrol at the concentration predicted in the water compartment would pose a hazard, particularly in view of its high water solubility and low partition coefficient.

15. RECOMMENDATIONS FOR SAFETY PROCEDURES TO CONTROL OCCUPATIONAL EXPOSURE

Due to the good safety profile of Isolutrol, only minimal control of worker exposure to this chemical is required. However, appropriate engineering controls and personal protection measures should be implemented to minimise worker exposure to the hydrocarbon solvent, methanol.

The following guidelines when followed will minimise occupational exposure to Isolutrol:

- the workplace should be well ventilated;
- suitable personal protective equipment which comply with Australian standards (AS) should be used:
    - chemical goggles (AS 1337) - *Eye Protectors for Industrial Applications* (24), in situations when splashing of the aqueous solutions of Isolutrol may occur;
    - disposal dust masks (AS 1716) - *Respiratory Protective Devices* (25), during the manual grinding of the dried Isolutrol; and
    - appropriate protective clothing;
- good work practice should be implemented to avoid spillages;
- good housekeeping and maintenance should be practised. Spillages of Isolutrol powder should be cleaned up promptly with a vacuum cleaner and disposed in accordance with local regulations;
- storage of Isolutrol should be in sealed containers which are kept in a dry environment at room temperature;
- a copy of the Material Safety Data Sheet should be accessible to employees.

16. RECOMMENDATIONS FOR MATERIAL SAFETY DATA SHEET (MSDS)

The MSDS for Isolutrol (Attachment 1) has been compiled according to Worksafe Australia format (26).

17. REQUIREMENTS FOR SECONDARY NOTIFICATION

Under the Industrial Chemicals (Notification and Assessment) Act 1989 (the Act), secondary notification of Isolutrol shall be required by McFarlane Marketing (Australia) Pty. Ltd. if any of the circumstances stipulated under subsection 64(2) of the Act arise. In addition, secondary notification is required when Isolutrol is to be formulated in cosmetic preparations in Australia.

18. REFERENCES

1. *Acute Oral Toxicity to Rats of Isolutrol (Active Ingredient)* - HRC Report No: 89478D/CNB 10/AC. Data on file, McFarlane Marketing Pty Ltd., (1989).

2. *Acute Oral Toxicity to Mice of Isolutrol (Active Ingredient)* - HRC Report No: 89477D/CNB 11/AC. Data on file, McFarlane Marketing Pty Ltd., (1989).

3. *Acute Intravenous Toxicity to Rats of Isolutrol (Active Ingredient)* - HRC Report No: 89476D/CNB 12/AC. Data on file, McFarlane Marketing Pty Ltd., (1989).

4. *Acute Intravenous Toxicity to Mice of Isolutrol (Active Ingredient)* - HRC Report No: 89475D/CNB 13/AC. Data on file, McFarlane Marketing Pty Ltd., (1989).

5. *Isolutrol Lotion: Acute Dermal Irritation/ Corrosion Test in the Rabbit* - LSR Report No: 88/CTA001/067. Data on file, McFarlane Marketing Pty Ltd., (1988).

6. *Isolutrol Lotion: Acute Eye Irritation/ Corrosion test in the Rabbit* - LSR Report No: 88/CTA002/084. Data on file, McFarlane Marketing Pty Ltd., (1988).

7. OECD Guideline for Testing of Chemicals - *Acute Oral Toxicity* No: 401 (1981).

8. OECD Guideline for Testing of Chemicals - *Acute Dermal Irritation/ Corrosion* No: 404 (1981).

9. Draize, J.H. et. al., *The Appraisal of Chemicals in Foods, Drugs, and Cosmetics*, Association of Food and Drug Officials of the United States, Austin, Texas (1959).

10. OECD Guideline for Testing of Chemicals - *Acute Eye Irritation/ Corrosion* No: 405 (1981).

11. *Irritant Effects of Repeated Dermal Application to Rabbit Skin of Isolutrol Lotion* - HRC Report No: 89268D/CNB 8/SE. Data on file, McFarlane Marketing Pty Ltd., (1989).

12. *Delayed Contact Hypersensitivity in the Guinea Pig with Isolutrol Lotion* - HRC Report No: 88384D/CNB 2/SS. Data on file, McFarlane Marketing Pty Ltd., (1988).

13. OECD Guideline for Testing of Chemicals - *Skin Sensitisation* No: 406 (1981).

14. Magnusson B. and Kligman A.M., *Allergic Contact Dermatitis in the Guinea-Pig: Identification of contact allergens*, Thomas C.C. Publ., Springfield, Illinois, USA.

15. *Ames Metabolic Activation Test to Assess the Potential Mutagenic Effect of Isolutrol - Active Ingredient* - HRC Report No: CNB 9/8993. Data on file, McFarlane Marketing Pty Ltd., (1989).

16. OECD Guideline for Testing of Chemicals - *Genetic Toxicology: Salmonella typhimurium, Reverse Mutation Assay* No: 471 (1983).

17. *An Androgenic Study of Isolutrol - (Scymnol sulphate)*. Data on file, McFarlane Marketing Pty Ltd., (1991).

18. *The Pharmacological Basis of Therapeutics*, 5th. Edition, Ed. L.S. Goodman and A. Gilman, Macmillan Publishing Company Inc., New York (1975).

19. *A Double Blind Randomised Three Stage Rising Dose Phase 1 Study to Determine the Safety, Irritation and Allergenic Potential of an Aqueous Solution of Isolutrol in Healthy Volunteers (Repeat Insult Patch Test)*. Data on file, McFarlane Marketing Pty Ltd., (1989).

20. *Human Photosensitisation Test.* Data on file, McFarlane Marketing Pty Ltd., (1989).

21. Kaidbey K.H. and Kligman A.N., *Photocontact allergy to 6-methylcoumarin*, Contact Dermatitis 4 (1978).

22. *Dangerous Properties of Industrial Materials*, 7th. Edition, Ed. N. Irving Sax and R.J. Lewis SR., Van Nostrand Reinhold Publ., New York, **2** (1989).

23. National Occupational Health and Safety Commission *Exposure Standards for Atmospheric Contaminants in the Occupational Environment*, Australian Government Publishing Service Publ., Canberra (1990).

24. Australian Standard 1337-1984 *Eye Protectors for Industrial Applications*, Standards Association of Australia Publ., Sydney (1984).

25. Australian Standard 1716-1984 *Respiratory Protective Devices*, Standards Association of Australia Publ., Sydney, (1984).

26. National Occupational Health and Safety Commission *Guidance Note for the Completion of a Material Safety Data Sheet*, 2nd, Edition, Australian Government Publishing Service Publ., Canberra (1990).