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NATIONAL INDUSTRIAL CHEMICALS NOTIFICATION AND ASSESSMENT SCHEME

FULL PUBLIC REPORT

ESTOL 3613

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Director
Chemicals Notification and Assessment

FULL PUBLIC REPORT

ESTOL 3613

1. APPLICANT

Unichema Australia, Pty Ltd, 164 Ingles St, Port Melbourne, Victoria.

2. IDENTITY OF THE CHEMICAL

Based on the nature of the chemical and the data provided, Estol 3613 is considered to be non-hazardous. Therefore, the chemical name, CAS number, molecular and structural formulae and the exact molecular weight have been exempted from publication in the Full Public Report and the Summary Report.

Trade name(s): Estol 3613

Molecular weight: <1000

Methods of detection and determination:

UV/VIS, IR and/or NMR spectra.

Spectral data: The IR spectrum exhibited major peaks at 1740 and 2930 cm^{-1}, the UV spectrum exhibited a peak at 212 nm and the NMR spectrum was consistent with structure.

3. PHYSICAL AND CHEMICAL PROPERTIES

Appearance at 20°C and 101.3 kPa: Virtually colourless liquid

Boiling Point: >200°C

Specific Gravity/Density: 860 kg/m^3

Vapour Pressure: <0.1 kPa at 25°C

Water Solubility:

Stated to be insoluble. The solubility of such fatty acid esters is generally considered to fall in the very low ppm range, but confirmatory data are sparse. The notifier estimates a solubility of 2 ppm by analogy with a similar fatty acid (1). This represents an overestimate, given that alkyl esters are more hydrophobic than their parent fatty acids. The calculated solubility, based on the estimated partition coefficient (see below), is 0.5 ppb (from equation 2-7 in reference 2).

Partition Co-efficient (n-octanol/water):

Not measured, but will be high as the parent fatty acid, which can be expected to be more hydrophilic than its alkyl esters, has a log P_{OW} >4 (3). Estimation by Leo's fragment method (2) provided a value of 9.2.

Hydrolysis as a function of pH:

The low solubility of the Estol 3613 retards its hydrolysis, but the chemical can be expected to hydrolyse about the ester linkage when in solution, or following absorption by living organisms.

Adsorption/Desorption:par
Not measured. Ethyl esters of pentanoic to octanoic acids have K_{OC} values increasing from 100 to 1000 (4). Estol 3613 can therefore be expected to sorb strongly to soil.

Dissociation Constant

Estol 3613 contains no readily dissociable groups.

Flash Point: Approx. 190°C (open cup)

Flammability Limits: Not flammable

Autoignition Temperature: >200°C

Explosive Properties: Not expected to be explosive

Reactivity/Stability: Stable under normal conditions. Avoid contact with strong oxidising agents.

Particle size distribution: Not applicable (liquid)

4. PURITY OF THE CHEMICAL

Degree of purity (of the notified chemical alone): >93%

Toxic or hazardous impurities: None

Non-hazardous impurity/impurities: (> 1% by weight)

Related fatty acid esters to 7%.

Additive(s)/Adjuvant(s): None

5. INDUSTRIAL USE

The notified chemical will be used in a solvent for printing ink removal in offset, cold set and heat set applications. It will be imported as a 50% formulation at 10 - 100 tonnes per annum for the first five years.

6. OCCUPATIONAL EXPOSURE

The formulation containing the notified chemical will be imported in 175 kg amounts in mild steel drums. Repacking of stock to 20 litre pails fitted with taps shall take place on site using a pumping system. Customer use will entail filling 1 litre wash bottles from the tap for cleaning printing machines.

A wash-up using the notified chemical is performed at the end of a print run or more frequently as necessary.

The wash-up procedure is as follows:

- the printing ink roller train is disengaged from the plate cylinder and rubber blanket which is used to transfer the plate image onto paper;

- a wash-up blade is connected to hinges ready for placing in contact with the roller train. The wash-up solution is squirted onto the roller train from a plastic squirt bottle. The wash-up blade is engaged onto the rollers and scrapes the ink residue/ solvent mix into a wash-up tray. More wash-up solution is added as required and the procedure is repeated;

- residue collected in the wash-up tray is wiped from the tray with rags which are placed in a receptacle for waste disposal; and

- the blanket is washed by placing the cleaning solvent onto a cloth and then wiping the blanket manually. The cloth is disposed of in the same way as the cloths used to clean the wash-up tray.

7. PUBLIC EXPOSURE

The sole intended use of Estol 3613 is in the printing industry, where it will be used in the cleaning of ink from printing machines. Release to the environment at printing sites will be negligible. Transport will be in mild steel drums (175 kg nett) and disposal (including rags) will be by chemical treatment and incineration. Estol 3613 is expected to be biodegradable.

8. ENVIRONMENTAL EXPOSURE

. Release

The blended product which contains about 50% Estol 3613, will be imported ready for use in mild steel drums (175 kg nett). The product is repacked into 20 L steel pails fitted with a tap and the pails are distributed to customers.

Rags contaminated with the ink residue/ solvent mixture will be disposed of by chemical treatment and incineration.

. **Fate**

The bulk of the ester blend used for cleaning printing equipment will be oxidised to carbon dioxide and water vapour when rags used for cleaning are burnt. Significant environmental exposure is therefore not expected; however, in the event of accidental spills to soil, significant leaching would not be envisaged in view of strong sorption and hydrolytic degradation. Spills to water can be expected to partition to sediment. Primary metabolites are fatty acids and a secondary alcohol, each of which occurs naturally, has widespread use, and is known (3) to undergo more extensive ultimate biodegradation. Bioaccumulation is not expected because of ready ester hydrolysis *in vivo*.

9. EVALUATION OF TOXICOLOGICAL DATA

No data using Estol 3613 were generated. The notifier has provided studies performed using related 2-ethylhexyl esters of saturated fatty acids of different chain length although some studies were provided in which Estol 1972 was used which contains 50% of the notified chemical.

9.1 Acute Toxicity

9.1.1 Oral Toxicity (5)

Of the studies provided for assessment, that concerning the acute oral toxicity of Estol 1972, which contains 50% of the notified chemical, is described here.

In this study 5 male and 5 female Wistar rats were given 5000 mg/kg of the test substance by gavage. No animals died during the 14 day observation period and no gross organ changes were seen. It was estimated that the LD_{50} value exceeded 5000 mg/kg body weight.

9.1.2 Dermal Toxicity (6)

A review was provided which contained the summary of a study on the acute dermal toxicity of a similar ester of 2-ethylhexanol.

In the study reviewed the undiluted substance was applied to the abraded and intact clipped skin of the trunk of each of 2 rabbits at doses of 0, 3.9, 6.0 and 9.4 mL/kg. The applied chemical was

held in place with a plastic sleeve for 24 hours after which the sleeve was removed and the animals observed for 14 days.

There were no deaths and no toxic effects were observed as measured by changes in urine, blood morphology or gross appearance. The LD_{50} is estimated to be >9.4 mL/kg body weight.

9.1.4 Skin Irritation (7)

The most relevant data were those obtained for Estol 1972.

Three young adult female New Zealand White rabbits were used for experimentation. The substance was applied to the clipped dorsal left flank of each animal in 0.5 mL amounts to 6 cm^2 gauze patches which then were covered with aluminium foil and finally wrapped in flexible bandages. After 4 hours the gauze patches and test substance were removed. Observations of erythema and oedema were made at 45 minutes, 24, 48 and 72 hours after substance removal.

The primary irritation index, calculated as the average Draize score for erythema plus oedema at 24 and 72 hours was 1.5 which is interpreted to mean that the substance is slightly irritating to rabbit skin.

9.1.5 Eye Irritation (8)

The most relevant data were those obtained for Estol 1972.

Three young adult female New Zealand White rabbits were used for experimentation. One hundred millilitres of undiluted Estol 1972 was instilled into the left eye of each rabbit. The lids were then gently held together for two seconds which resulted in the extrusion of some of the test substance. Eyes were examined 1, 24, 48 and 72 hours after instillation. The only positive Draize scores occurred in two rabbits 1 hour after instillation. In each case a conjunctival redness score of 1 was noted as an indication that some blood vessels were definitely hyperaemic or injected.

It is concluded that Estol 1972 is practically non-irritating to the rabbit eye.

9.1.6 Skin Sensitisation (6, 9)

A review was provided in which the sensitisation potential of an ester of 2-ethylhexanol was described (6) and a study on the skin sensitisation potential of another ester of 2-ethylhexanol was provided.

With regard to reference 6, two studies were reviewed in which the substance was dissolved in olive oil or suspended in sterile, pyrogen-free saline. In both cases 10 white male guinea pigs had their backs and flanks clipped free of hair prior to injection of a 0.1% solution or suspension, 3 times weekly until a total of 10 injections had been made. The first injection was 50 µL and the remaining nine were 100 µL. Two weeks after the 10th injection a challenge injection of 50 µL of a freshly prepared solution or suspension was made slightly below the area where the induction injections had been made. The challenge site was evaluated after 24 hours. In both studies, it was concluded that the substance was not a sensitiser.

In the study outlined in reference 9, a guinea pig maximisation test was performed.

A preliminary dose range finding study was performed to find the minimal irritant dose following intradermal injection to use for induction. A similar study was performed to find an appropriate percutaneous induction dose and an appropriate challenge dose which caused no irritation.

For each of 10 guinea pigs, six 0.1 mL intradermal injections were made close together within a 8 cm^2 area of the shoulder region; 2 injections of the test substance in solvent; 2 injections of the test substance in Complete Freund's Adjuvant (CFA); and 2 injections of 50% CFA in saline. Seven days later the induction was repeated by placing over the injection site a filter paper patch saturated with the test substance at the selected concentration.

Fourteen days after the application of the shoulder patch, the guinea pigs were challenged on the flank by an occluded patch containing the test substance. Twenty four hours after the patch was secured in place, it was removed. The reaction site was examined 24 and 48 hours after removal of the patch.

Appropriate positive and negative controls were included and gave the expected responses. Following challenge, no sensitisation was observed in animals induced with the test substance.

9.2 Repeated Dose Toxicity (6)

A review was provided in which studies on the repeated dose toxicity of an ester of 2-ethylhexanol were described (6).

In one study the substance was applied in doses of 1.0 mL/kg by gentle inunction to the shaved skin of 10 male and 10 female albino rats. Applications were made five days a week for a total of 27 applications in 6 weeks. No significant changes in general appearance or behavior were observed, nor were any toxicologic signs noted. Also, no significant pathological changes of toxicological significance were noted.

A second study was conducted over 60 days and the substance was applied undiluted. The substance was applied daily to an 80 cm^2/kg area on the shaved back and flanks of each of three albino rabbits. The ingredient was "poorly tolerated" in two of the three rabbits, and histological examination showed congestive dermatitis in three of six biopsies (two from each animal). The applied dose was not stated and it is not clear from the description whether any systemic effects were observed.

9.3 Genotoxicity and Teratogenicity

A published paper (10) reported the mutagenic responses of 25 cosmetic ingredients including fatty acid ester similar to the notified substance and the results were negative.

Other than this the notifier contended that Estol 3613 would be quickly metabolised (hydrolysed) *in vivo* to 2-ethylhexanol and a fatty acid. Direct evidence for this was not presented but a reference was cited showing that rat liver and intestinal extracts readily hydrolysed 16 flavouring esters in vitro (11), and a text book excerpt on esters of fatty acids (12), supported the contention.

The parent fatty acid of Estol 3613, like other fatty acids, is a natural constituent of edible oils and fats. The human population is therefore exposed to these compounds via the diet.

2-Ethylhexanol, however, has been identified as a putative teratogen and, because it is a metabolite of di-2-ethylhexyl phthalate (DEHP - a peroxisome proliferator and suspected carcinogen), has been subjected to a series of genotoxicity tests. The sponsor provided a series of published papers addressing the genotoxicity and teratology of 2-ethylhexanol.

2-Ethylhexanol has been shown to be nongenotoxic toward *Salmonella typhimurium* strains TA 98, TA 100, TA 1535, TA 1537 and TA 1538, in the presence or absence of metabolic activation (13, 14, 15), and in *E. coli* strain WP2 *uvrA* (14). 2-Ethylhexanol has also been shown to be negative in mouse lymphoma L5178Y cells (TK+/- locus) and in a transformation assay using mouse epidermis-derived JB6 cells *in vitro* (16). No evidence for chromosomal damage was seen in Chinese hamster ovary cells, although no metabolic activation system was used in this assay (17).

A weak positive response (<3 fold increase in mutants/ cell over controls) was seen when 2-ethylhexanol (0.5 - 1.5 mM) was incubated with *S. typhimurium*, and a variant end-point was examined (8-azaguanine resistance rather than histidine independence) (18). The absolute numbers of mutants was not increased and the apparent positive response appeared to be related to reduced survival rather than a direct mutagenic effect. This artifact stems from the fact that the number of spontaneous mutants remains constant as cell survival decreases and the mutation frequency is calculated per cell rather than per survivor.

As to the developmental toxicity of 2-ethylhexanol, a number studies have been reported in the literature and these are summarised here.

(i) Mice (gavage) - Screening study (19).

2-Ethylhexanol (1525 mg/kg/d) was administered to 49 pregnant CD-1 mice during days 6-13 of gestation. This was a maternotoxic dose, causing in dams, 17 deaths, reduced weight gain and reduced viable litters. Numbers of live-born/litter, birth weight and pup weight gain were significantly reduced. Malformations were not examined.

(ii) Rats (gavage) (20).

2-Ethylhexanol (1 or 2 mL/kg, approximately equivalent to 2000 or 4000 mg/kg) was administered to groups of 7 pregnant Wistar rats on day 12 of gestation. These doses were not maternotoxic. Animals were killed on day 20 of gestation. The percentage of fetuses dead or resorbed was not affected but 22% of surviving pups were malformed in the HD group, with hydronephrosis and limb defects being the most common malformations. No effect was observed in LD pups.

(iii) Rats (vapour) (21).

Pregnant Sprague-Dawley rats were exposed to 2-ethylhexanol vapour (850 mg/m^3) 7 h/day during days 1-19 of gestation. This was the maximum vapour dose possible and was not maternotoxic. Animals were killed on day 20. No foetal malformations were observed.

(iv) Rats (dermal) (22).

Undiluted 2-ethylhexanol was administered by occluded dermal application for 6 hours per day on gestation days 6 through 15 to pregnant Fischer 344 rats in range-finding and main studies. In the main study, levels were 0, 252, 840 and 2520 mg/kg/day. Appropriate negative and positive controls were included and gave the expected responses. The no adverse effect level for systemic toxicity was 840 mg/kg/day. 2-Ethylhexanol was not developmentally toxic or teratogenic in this experiment.

9.5 Overall Assessment of Toxicological Data

No data for the notified chemical as such were provided. However, data for the related substance Estol 1972 containing 50% of the notified chemical was provided. This chemical exhibited very low acute oral toxicity, was slightly irritating to rabbit skin and was practically non-irritating to the rabbit eye.

A repeated dose toxicity study with a related ester of 2-ethylhexanol suggested the possibility of some effects of dermal application at high dose levels for a long period, notably congestive dermatitis.

Two related esters of 2-ethylhexanol were non-sensitisers suggesting, by analogy, that the notified chemical has a low sensitisation potential.

The fact that esters of a similar nature to the notified chemical are negative in the Ames test suggests, by analogy, that the notified chemical would also be negative.

The notifier provided evidence that the notified chemical would likely be rapidly metabolised to 2-ethylhexanol and the parent fatty acid *in vivo.* As the parent fatty acid is a normal constituent of the diet, chronic exposure to this chemical already occurs in the human population. Evidence was provided that 2-ethylhexanol was not genotoxic in the Ames test, in the mouse lymphoma mutagenicity test, in a mouse epidermal cell transformation assay or in a Chinese Hamster Ovary cell chromosome aberration assay although no metabolic activation system was used in this assay.

2-Ethylhexanol was teratogenic in rats given 2 mL/kg/day on day 12 of gestation and showed developmental toxicity in mice (at a maternotoxic dose). When administered to rats via the inhalational or dermal routes, during the period of organogenesis, no adverse effects on fetuses were noted.

10. ASSESSMENT OF ENVIRONMENTAL EFFECTS

In general, hydrophobic chemicals consisting primarily of carbon with isolated heteroatoms or functional groups become non-lethal to fish under conditions of acute exposure when the number of carbons exceeds 12-14 (23). Exceptions may occur where highly polar functional groups depress the (log) partition coefficient below 5.5, much lower than the estimated value of 9.2. On the basis of its structure and published toxicity data (23) for industrial esters, Estol 3613 would not be expected to exert toxic effects at concentrations below its solubility limit, or even several orders of magnitude above it.

11. ASSESSMENT OF ENVIRONMENTAL HAZARD

The predicted environmental hazard arising from use of Estol 3613 in the printing industry is minimal as the use and disposal

pattern is not expected to lead to significant environmental exposure, accumulation and bioaccumulation are not envisaged, and the toxicity appears low.

12. ASSESSMENT OF PUBLIC AND OCCUPATIONAL HEALTH AND SAFETY EFFECTS

It is expected that public exposure to the notified chemical will be minimal.

In the occupational setting, exposure would be expected to be mainly to the skin and to occur in cleaning spills, filling wash bottles and cleaning the rubber mat which transfers the ink image to paper in the printing process.
Based on experiments with a substance containing 50% of the notified chemical, the notified chemical is likely to exhibit very low acute oral toxicity and would be expected to be of very low acute dermal toxicity based on studies with a related ester of 2-ethylhexanol. Due to the low vapour pressure of the notified chemical, inhalational exposure is not expected under conditions of normal use.

With regard to repeated dose toxicity, a review of some data on a related ester of 2-ethylhexanol suggested that there would be some effect of heavy exposure for a long period of time. These results suggest that precautions should be taken to minimise exposure as outlined in section 13. However, under normal conditions of use, where exposure occurs for a short period of time at the end of a print run, effects should be minimal. It is also expected that no spray would be generated under conditions of normal use.

Based on studies with Estol 1972, which contains 50% Estol 3613, the notified chemical would be expected to be minimally irritating to the skin and practically non-irritating to the eye.

Based on studies with two related esters of 2-ethylhexanol, the notified chemical would not be expected to be a skin sensitiser.

The notifier did not provide any data on the genotoxicity of the notified chemical. Other fatty acid esters were found to be negative in the Ames test which suggests that the notified chemical is also likely to be negative in this assay.

The notifier argued that the notified chemical would be metabolised to 2-ethylhexanol and the parent fatty acid *in vivo* and there is some support for this contention in the literature (11, 12). As the parent fatty acid is a normal constituent of the diet, it is expected that exposure from this source would be greater than that from use of the notified chemical.

A number of studies have shown that 2-ethylhexanol is not genotoxic. However, there is some evidence that this chemical may be teratogenic in rats at very high doses when administered orally but not dermally. This suggests that dermal exposure to the notified chemical is highly unlikely to result in teratogenic effects.

13. RECOMMENDATIONS

To minimise occupational exposure to Estol 3613 the following guidelines and precautions should be observed:

- during prolonged contact with Estol 3613, personal protection devices which comply with Australian Standards (AS) such as safety glasses (AS 1336; AS 1337) (24, 25), impermeable gloves (AS 2161) (26) and protective clothing (AS 3765.1, 3765.2) (27, 28) should be worn;

- good work practices should be implemented to avoid spillages and splashing;

- good housekeeping and maintenance should be practised. Spillages should be cleaned up promptly with absorbents which should then be put into containers for disposal in accordance with local or State regulations;

- good personal hygiene should be observed; and

- a copy of the Material Safety Data Sheet should be easily accessible to employees.

14. MATERIAL SAFETY DATA SHEET

The Material Safety Data Sheet (MSDS) for Estol 3613 was provided in Worksafe Australia format (29).

15. REQUIREMENTS FOR SECONDARY NOTIFICATION

Under the *Industrial Chemicals (Notification and Assessment) Act 1989* (the Act), secondary notification of Estol 3613 shall be required if any of the circumstances stipulated under subsection 64(2) of the Act arise. No other specific conditions are prescribed.

16. REFERENCES

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