Classification Submitted

5-ethylidene-8,9,10-trinorborn-2-ene (CAS: 16219-75-3. EC: 240-347-7)

Classification and risk phrase(s) according directive 67/548 based on data in dossier – substance not listed in Annex I	**Classification as indicated by the available data that is to be included in the IUCLID dossier submission according to regulation 1272/2008. Signal word, pictogram, Hazard class and statement codes ***
Harmful R10; Xn: R20, R65; Xi: R38, R43; N R51/53	Danger: GHS02, GHS07 Flammable liquid cat 3: H226 Acute tox 4: H332 Aspiration hazard cat 1: H304 Skin irritant cat 2: H315 Skin sensitization cat 1: H317 STOT (RE): H373 Hazardous to aquatic environment chronic cat 2: H411
Flammable Harmful by inhalation Harmful: May cause lung damage if swallowed Irritating to skin May cause sensitisation by skin contact Toxic to aquatic organisms; may cause long term adverse effects in the aquatic environment.	Flammable liquid and vapour Harmful if inhaled. May be fatal if swallowed and enters airways Causes skin irritation May cause an allergic skin reaction May cause damage to organs through prolonged or repeated exposure Toxic to aquatic life with long lasting effects
	
Special concentration limits >3%, Xi R43	Special concentration limits >3% H317

Justification :

Physicochemical properties

Flashpoint re-measured and determined to be in 28.5C, which warrants classification as shown in the table above.

Acute toxicity

There are a number of acute toxicity studies on ENB by the inhalation route, the oral route and the dermal route. The acute oral LD_{50}value was 2276 mg/kg for male rats and 5071 mg/kg for female rats. The acute inhalation LC_{50}values were 13.3 mg/L (2717 ppm) for male rats and 14.8 mg/L (3015 ppm) for female rats. The dermal LD_{50} value was greater than 7168 mg/kg for male and female rabbits.

Based on the available animal data, there is sufficient information available to determine that no classification is required for the oral and dermal routes of acute exposure. For the inhalation route, the data available indicates that classification as harmful by inhalation is required under directive 67/548. Under regulation 1272/2008, the rat (average of results from all studies and sexes), rabbit and guinea pig data would indicate classification as harmful. The data on mice suggest a classification as toxic. However, a classification based on the response in the majority of species and therefore a classification of harmful seems most appropriate. This is pragmatically supported by the observation that the range of LC50 values span the range 13 -56% of the saturated vapour concentration at 20C. The rat is also the named species for acute classification of inhalation toxicity and data from the rat indicates classification as harmful only.

Skin irritation

Occluded contact with 0.5 ml of undiluted ENB for 4 hrs produced mild to moderate erythema and edema on rabbit skin, which resolved within 7-14 days; necrosis was not seen. Average erythema score >2.

From the available data, the level of skin irritation, as measured by erythema, indicates classification as a skin irritant under directive 67/548 is warranted. Individual animal data is not available to enable a definitive classification against the criteria in regulation 1272/2008. However, it is quite conceivable that 2 or the 3 animals would have produced more severe reactions and therefore a similar classification (category 2 skin irritant) under this regulation would seem appropriate.

Skin sensitisation

The results from a mouse LLNA study indicate that ENB should be classified as a skin sensitiser. The stimulation index was as follows at the concentrations shown: 25%v/v: 2.16 (Negative); 50%v/v: 3.42 (Positive); 100% v/v: 7.22 (Positive). This quantitative data indicates that the response is weak and, according to the recommendations of ECETOC ("Contact Sensitisation: Classification according to potency", Technical Report 87, 2003) such a response would justify a classification limit for mixtures of 3% rather than the default of 1%. This limit is proposed for inclusion.

Aspiration hazard

The substance is a hydrocarbon and has a viscosity well below the cut off for classification. Classification is therefore warranted.

Repeat dose effects

There are no sub-chronic repeat dose studies available by the oral route of exposure. There is a sub-acute 28-day repeated oral dose toxicity test available. Sprague-Dawley rats received doses of 0, 4, 20 and 100 mg/kg/day for 28-d by oral gavage.

In the 100 mg/kg group females the mean body weight was significantly reduced at dosage termination but not in the recovery group. Food consumption was not affected. Urinalysis revealed an increase in the number of animals with protein-positive urine and a decrease in water consumption in males given 100 mg/kg. These changes were not found at the end of recovery period. In the hematological examination, no effect was observed after administration of ENB. In the blood biochemical examination, 20 and 100 mg/kg group

males showed a decrease in alpha-1 globulin level. However, these changes were not found at the end of the recovery period. In high dose males there was increased brain/body wt ratio and increased kidney/body wt ratio; both effects were absent in recovery males. At autopsy, pale discoloration of the kidneys was observed in males given 100 mg/kg, and histopathology showed increased hyaline droplets in renal tubule epithelium of all male rats in the 20 and 100 mg/kg groups. Histopathological examination of the thyroid indicated hypertrophy of follicular epithelium, as well as decrease in colloid or irregular shape of follicles in males given 4 mg/kg or more. Hypertrophy of follicular epithelium and decrease in colloid were also observed in females given 100 mg/kg. There were no effects on the testes. The NOAEL of ENB for repeated dose toxicity was reported to be less than 4 mg/kg/day for males (based on thyroid effects at 4 mg/kg and kidney effects at 20 mg/kg) and 20 mg/kg/day for females (based on thyroid effects at 100 mg/kg). However, the male rat kidney effects are consistent with alpha-2u-globulin nephropathy and are not considered to be relevant to humans. The thyroid effects are also likely to be a species specific effect not relevant to humans. For these reasons, the oral NOAEL based on systemic effects other than thyroid and kidney is 20 mg/kg/d, based on reduced body weight of females in the 100 mg/kg/d group.

There are no repeat dose studies available by the dermal route of exposure.

There are four inhalation repeated dose toxicity studies of ENB. One study was of less than 2 wk duration and served as a range finding study for a 14 week subchronic study. The early studies, with limited monitoring, showed that exposure to high concentrations (e.g., 237 ppm) of ENB vapor produced liver, kidney, and testicular injury in the rat accompanied by a high incidence of mortality, and liver and testicular injury in the dog. In the more recent rat studies where the purity of the ENB was measured and exposure concentrations maintained at or below 149 ppm, there is no biochemical or histologic evidence for testicular effects, minor adaptive and reversible changes in the liver, and male-rat specific kidney effects. Thyroid effects were evaluated in the rat oral 28-d study and the rat inhalation 14-wk study. These two were selected as key studies and considered to be the most reliable because they were conducted under well-designed protocols, reported analytical purity of the test material, and detailed information is available in the study reports. An observation common to these two studies are thyroid changes which are considered likely to be a species specific effect not relevant to humans.

The NOAEL for repeated oral dose toxicity in rats is considered to be 20 mg/kg/day for male and female rats, based on the 28-d oral toxicity study. Based on the 14-wk inhalation study, the NOAEL for repeated inhalation toxicity in the rat is 24.8 ppm (122 mg/m^3). These values are based on systemic effects other than thyroid and kidney, which are not considered relevant to humans.

On the basis of reliable animal data, no effects have been observed which warrant classification under directive 67/548.

Under regulation 1272/2008, a classification for STOT (RE) category 2 could be considered appropriate as a LOAEL of 0.75mg/l (150ppm) was established in a sub-chronic study. However, the only effects seen were increases in liver and kidney weight without associated changes to histopathology and changes to urinary parameters of unknown toxicological significance. Other effects noted at this or lower concentrations were established as reversible. Therefore no 'significant' toxic effects were seen and therefore classification under 1272/2008 is not warranted based on this study. However, the data from older studies

reported adverse findings (LOAEL) of 61ppm (0.305mg/l) in both rats and dogs. These changes were associated with adverse histopathology as well. These findings could be considered 'significant' and therefore, on a precautionary basis, a STOT classification (category 2) would appear warranted and is proposed.

Environmental effects

The substance is not readily biodegradable. The acute toxicity is moderate with LD50/EC50 values consistently in the range 1 -10mg/l. On this basis classification as toxic to the environment appears to be justified (N: R51/53 under directive 67/549 and Chronic category 2: H411 under regulation 1272/2008.)

Other end points

The available data did not indicate a need to classify for any other end point.