

Psyed

FYI-0496-1270S

Document Processing Center (7407)
Attn: Section 8(e) Coordinator
Office of Pollution Prevention & Toxic Substances
U.S. EPA
401 M Street, S.W.
Washington, D.C. 20460

*Company -
Sanitized*

Re: PMN []

The following information has come to [] attention as the result of toxicity testing being conducted for registration under the European Union's 7th Amendment to the Hazardous Substances Directive. [] does not believe the results of these tests trigger the Section 8(e) reporting requirement for substantial risk. EPA guidance states that effects that are transient and reversible are not reportable; the guidance also indicates lethargy and increased salivation are not reportable effects. However, [] is forwarding these test results to EPA for the agency's information.

The testing information has been developed for [] generically identified as Trifunctional ketoximino silane, which is the subject of PMN [].

Preliminary results of a 28-day oral rat gavage study with recovery at doses of 15, 150 and 500 mg/kg administered daily indicate signs of transient narcosis and anemia. The transient narcosis occurred at the high dose level (500 mg/kg). The anemia was clinically apparent at the mid and high dose levels (150, 500 mg/kg) and microscopically evident at the low dose level (15 mg/kg). All of the above effects were considered reversible based upon observation of the recovery animals.

In addition, some microscopic changes identified consisted of centrilobular hepatocytic enlargement and pigmentation and inclusions in the cortical tubules of the kidney. These effects may be related to the anemia.

Best regards,

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(Report of results - continued)

Four-week oral toxicity study with two-week recovery period (Report number ALS 66/952297)

| Administration period | | From 8 August 1995 to 22 September 1995 | | | | Number of animals per group | |
|--------------------------|------------------|---|---------------|------------------|---------------------------|-----------------------------|---------|
| Animal species/strain | | Charles River rat, CrI: CD ⁰ BR VAF Plus | | | | Males | Females |
| Route of administration | | Oral Gavage | | | | Recovery group | |
| Purity of test substance | > 92% | Dose level (mg/kg/day) | Control group | Low dosage group | Intermediate dosage group | High dosage group | |
| | | | | 0 | 15 | 150 | 500 |
| | | | ♂ | ♂ | ♂ | ♂ | ♂ |
| | | | ♀ | ♀ | ♀ | ♀ | ♀ |
| Clinical signs | Treatment period | | - | - | (c) | a, b, (c) | a, (c) |
| | Recovery period | | - | - | - | - | - |
| Bodyweight change | Treatment period | | (v) | - | - | v | - |
| | Recovery period | | - | - | - | - | - |
| Food consumption § | Treatment period | | - | - | - | - | - |
| | Recovery period | | - | - | - | - | - |
| Water consumption § | Treatment period | | - | - | - | - | - |
| | Recovery period | | - | - | - | - | - |

§ Statistical analysis not performed
 a Loss of muscle tone, ictergry
 b Prostration
 c Increased salivation and wet fur
 0 Denotes a statistically significant difference of a finding that was not considered to be related to treatment
 v Significantly decreased in comparison with the controls

Revised

(Report of results - continued)

Four-week oral toxicity study with two-week recovery period

| Administration period | | | From 8 August 1995 to 22 September 1995 | | | | | | | | | | | | |
|------------------------------|------|------------------------|--|---|------------------|-----|-----------------------------|---------|-------------------|-----|------------------|---|-----|---|-----|
| Animal species/strain | | | Charles River rat, Cri: CD [®] BR VAF Plus | | | | Number of animals per group | | | | | | | | |
| Route of administration | | | Oral gavage | | | | Males | Females | | | | | | | |
| Purity of test substance | >92% | Dose level (mg/kg/day) | Control group | | Low dosage group | | Intermediate dosage group | | High dosage group | | Recovery group + | | | | |
| | | | 0 | | 15 | | 150 | | 500 | | 0 | | 500 | | |
| | | | ♂ | ♀ | ♂ | ♀ | ♂ | ♀ | ♂ | ♀ | ♂ | ♀ | ♂ | ♀ | |
| Blood haematology findings: | | | PCV | | - | - | ▼ | ▼ | ▼ | ▼ | | ▲ | ▲ | | |
| | | | Hb | | - | - | ▼ | ▼ | ▼ | ▼ | | ▲ | ▲ | | |
| | | | RBC | ▲ | | - | - | ▼ | ▼ | ▼ | ▼ | | - | ▼ | |
| | | | MCHC | | | - | - | - | ▼ | ▼ | ▼ | | - | ▼ | |
| | | | MCV | | | - | - | ▲ | ▲ | ▲ | ▲ | | ▲ | ▲ | |
| | | | MCH | | | | | ▲ | ▲ | ▲ | ▲ | | ▲ | ▲ | |
| | | | Platelets | | | | | | | - | - | ▲ | | - | - |
| | | | Eosinophils | | | - | - | - | - | ▼ | ▼ | | | - | - |
| Blood biochemistry findings: | | | Triglyceride | | | - | - | - | - | ▲ | | | - | | |
| | | | GPT | | | - | - | - | - | ▼ | - | | | - | |
| | | | Urea nitrogen | | | - | - | - | - | ▲ | - | | | - | |
| | | | Glucose | | | - | - | - | - | ▼ | - | | | - | |
| | | | Phosphorus | | | - | - | - | - | ▲ | - | | | - | |
| | | | K | | | - | - | - | - | ▲ | ▲ | | | - | |
| | | | Bilirubin | | | - | - | ▲ | - | ▲ | ▲ | | | - | (▼) |
| | | | AP | | | (▼) | - | (▼) | - | (▼) | - | | | | - |
| Albumin | | | - | - | - | - | (▲) | - | | | | - | | | |

- ▲ Significantly increased in comparison with controls (P < 0.05)
▼ Significantly decreased in comparison with controls (P < 0.05)
▲ Significantly increased in comparison with controls (P < 0.01)
▼ Significantly decreased in comparison with controls (P < 0.01)
+ Results for recovery period only
() Denotes a statistically significant difference or a finding that was not considered to be related to treatment

fold

(Report of results - continued)

Four-week oral toxicity study with two-week recovery period

| Administration period | | | From 8 August 1995 to 22 September 1995 | | | | | | | | | | | | | |
|---------------------------------------|-------|------------------------|--|-----|------------------|-----|-----------------------------|-----|-------------------|-----|------------------|-----|-----|-----|-----|-----|
| Animal species/strain | | | Charles River rat, Cri: CD [®] BR VAF Plus | | | | Number of animals per group | | | | | | | | | |
| Route of administration | | | Oral gavage | | | | Males | | Females | | | | | | | |
| Purity of test substance | > 92% | Dose level (mg/kg/day) | Control group | | Low dosage group | | Intermediate dosage group | | High dosage group | | Recovery group + | | | | | |
| | | | 0 | | 15 | | 150 | | 500 | | 0 | | 500 | | | |
| | | | ♂ | ♀ | ♂ | ♀ | ♂ | ♀ | ♂ | ♀ | ♂ | ♀ | ♂ | ♀ | | |
| Histological findings: | | | a | - | - | - | - | 1/5 | 2/5 | 4/5 | 2/5 | - | - | 1/5 | 3/5 | |
| | | | b | - | - | - | 1/5 | - | 2/5 | 2/5 | 2/5 | - | - | 3/5 | 5/5 | |
| | | | c | 2/5 | - | 5/5 | - | 5/5 | - | 5/5 | - | 5/5 | - | 5/5 | - | |
| | | | d | - | - | - | - | - | - | 4/5 | 5/5 | - | - | 4/5 | 5/5 | |
| | | | e | - | - | - | 4/5 | 5/5 | 5/5 | 5/5 | 5/5 | 5/5 | 2/5 | 5/5 | 5/5 | 5/5 |
| | | | f | - | - | 2/5 | 1/5 | 4/5 | 4/5 | 5/5 | 5/5 | - | - | - | - | |
| | | | g | - | - | - | - | 2/5 | - | 5/5 | - | - | - | - | - | |
| NOAEL/NOEL (mg/kg/day): | | | A no observed adverse effect level NOAEL and a no observed effect level NOEL could not be established in this study. | | | | | | | | | | | | | |
| Change(s) by which NOAEL is estimated | | | Evidence of haemolysis of red cells at 15 mg/kg/day (namely extramedullary haemopoiesis and haemosiderosis in the spleen and pigmented sinusoidal cells in the liver) was considered to be an adverse effect | | | | | | | | | | | | | |

- + Results for recovery period only
- a Liver-centrilobular hepatocyte enlargement
- b Pigmented sinusoidal cells
- c Kidneys - cortical tubules with eosinophilic inclusions
- d Kidneys - cortical tubules with golden brown granular pigment
- e Haemosiderosis in the spleen (minimal/moderate)
- f Extramedullary haemopoiesis of the spleen (moderate)
- g Congestion of the spleen

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