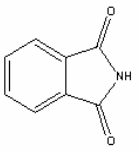
SIDS INITIAL ASSESSMENT PROFILE

CAS No.	85-41-6
Chemical Name	Phthalimide
Structural Formula	

SUMMARY CONCLUSIONS OF THE SIAR

Human Health

Comprehensive data on toxicokinetic, metabolism, or distribution are not available. In a limited animal study placental transfer of phthalimide is demonstrated.

The acute toxicity of phthalimide has been well characterized and is generally low. Reduced appetite, reduced activity and slight lethargy for one to three days are the only effects observed in animals dosed with 7940 mg/kg bw by the oral or dermal route.

In animal experiments phthalimide is slightly irritating to the skin or the eye. Observed effects are reversible within 2 to 3 days.

Phthalimide is of low repeated dose toxicity. In a sub-acute inhalation study in rats the NOAEL for males is estimated to be 523 mg/m^3 (highest dose tested), and in females the NOAEL is 154 mg/m^3 based on the significant lower lung to body weight ratio in the 523 mg/m^3 dose group, although no histopathological alteration of the lung was observed at any dose. Oral repeated dose toxicity was investigated in a recent guideline study (OECD TG 422). No compound related effects were observed in male rats dosed with up to 1000 mg/kg bw/day (highest dose tested). In one female rat given 1000 mg/kg bw/day food consumption and body weight were decreased, and histopathological examination revealed peritoneal fatty changes in the liver, renal epithelial fatty changes, and atrophy in the thymus. Consequently, the NOEL for oral repeated dose toxicity is considered to be 500 mg/kg bw/day for females and 1000 mg/kg bw/day for males (highest dose tested).

Phthalimide is not active in a variety of mutagenicity tests *in vitro*. It is not mutagenic in "bacterial reverse mutation test" (OECD TG 471, and 472) in the presence and absence of metabolic activation system (S9-mix). It does not induce mutations in the mouse lymphoma assay. In the chromosomal aberration test (OECD TG 473) no polyploidy is observed at any concentration in the absence and presence of metabolic activation. Weak clastogenic effects are observed in the presence of metabolic activation at high concentrations where cytotoxicity is seen in parallel. Genotoxicity studies *in vivo* are not available. Overall phthalimide is considered to be not genotoxic *in vitro* and based on the available data it is anticipated that it will not be genotoxic *in vivo*.

In the previously described "combined repeated dose toxicity study with the reproduction/developmental toxicity screening test" (OECD TG 422) the NOEL for reproductive and developmental toxicity is 250 mg/kg bw/day, based on the observation that pups in the 500 and 1000 mg/kg bw/day groups showed slightly reduced body weights or lower body-weight gains in the lactation period at day 4, and that 8 pups were dead or cannibalized and the surviving 9 pups showed body weight loss in one female dosed with 1000 mg/kg bw/day with abnormal histopathological

findings.

No evidence for embryonic/fetal lethality or teratogenicity was seen after oral application to hamsters as well as in two oral studies in rabbits both being limited by an insufficient study design: either low number of animals tested and only external malformations evaluated or only a single dose tested.

Environment

Phthalimide forms white crystalline leaflets with a melting point of 238 °C. For the boiling point it was reported both sublimation and a measured value of > 350 °C at 1013hPa (OECD TG 103). The measured density is 1.455 at 25 °C, the measured vapor pressure is 0.00056 Pa at 25 °C (OECD TG 104), the measured log K_{ow} 1.15. The measured solubility in water is 370 mg/l at 25 °C. The flash point is 214 °C, the auto flammability (ignition temperature) 530 °C. Phthalimide is a weak acid with a pK_a of 8.3.

In the atmosphere phthalimide is degraded by photochemically produced OH radicals. The half-life is calculated to be ca. 2.6 days. Removal of phthalimide in rain water and soil was influenced by light. Phthalimide is expected to hydrolyze in the hydrosphere to phthalic acid and ammonia with phthalamic acid being an intermediate. According to a test performed according to OECD TG 111, hydrolysis is faster in basic solution with a half-life of 1.1 h at pH 9; $t_{1/2}$ at pH 7 is 57 h, and at pH 4 is 115 days. Phthalimide is readily biodegradable with a biodegradation rate of 92 % after 14 days [OECD TG 301C]. In a Zahn-Wellens test 96.2 % phthalimide were degraded within 5 days, and in a test using acclimated activated sludge 63-88 % were degraded within 24 h.

According to the Mackay fugacity model level I, the favourite target compartments of phthalimide are water with 99.8 %, followed by sediment and soil with both 0.1 %. The calculated Henry's law constant 1.03×10^{-3} - 0.22×10^{-3} Pa m^3/mol at 25 °C, proves a very low potential for volatilisation from surface waters.

The calculated BCF of 1.53 and the experimental bioconcentration factors of 4.6-8.5 at 1.0 mg/l and 4.7-22 at 0.1 mg/l phthalimide, respectively, measured in the fish *Cyprinus carpio* [method similar to OECD TG 305], indicate no significant bioaccumulation potential.

No experimental data on geoaccumulation is available. The calculated K_{oc} values of 10.75-10.84 indicate a low sorption potential of phthalimide onto the organic phase of soil or sediments.

Concerning the acute toxicity of phthalimide towards aquatic species, experimental results for the three trophic levels are available. The lowest valid results of phthalimide for each aquatic trophic level are the following (n = nominal concentration, e = mean measured concentration):

Salmo gairdneri (fish)	96 h-LC_{50} = 51 mg/l (n)
Daphnia magna (aq.invertebrate):	48 h-EC_{50} = 21 mg/l (e)
Selenastrum capricornutum (algae):	72 h-E_bC_{50} = 33 mg/l (e)
	72 h-E_rC_{50} = 161 mg/l (e)
Pseudomonas putida (bacteria):	16 h-EC_0 = 260 mg/l (e)

Results on chronic toxicity towards *Daphnia* and algae are available as well:

Daphnia magna (aq.invertebrate):	21 d-NOEC = 7.6 mg/l (e)
Selenastrum capricornutum (algae):	72 h-$NOEC_b$ = 0.6 mg/l (e)
	72 h-$NOEC_r$ = 10.7 mg/l (e)

No standard tests on toxicity towards terrestrial plants are available. Phthalimide and phthalimide potassium salt were shown to increase vigour of plants *Fragaria ananassa* and *Datura metel* respectively. The derivative of phthalimide, phthalimide potassium salt was additionally reported not to be toxic towards *Datura metel*. Other available results:

Lactuca sativa (plant):	3 d-EC_{50} = 34 mg/l (n)	[endpoint germination]
Bufo bufo japonicus (amphibian):	24 h-$LC_0 \geq$ 42 mg/l (n)	[toad tadpole toxicity]

Exposure

Phthalimide is obtained by heating phthalic anhydride with ammonia. The resulting product is often not isolated but directly converted. In 1998, the global production capacity of isolated phthalimide is estimated to be more than 8,000 tonnes/a, located in the EU. Another approximately 18,000 tonnes/a worldwide is converted directly to anthranilic acid (capacities in tonnes/a): Germany 10,000, UK 2,000, Japan 500, USA 6,000, India 120, and China <300. In Germany, there is one production site for isolated phthalimide with an estimated manufacturing capacity of 2,500 tonnes/a. In Japan, the manufacturing volume is 1000-2000 tonnes/a.

Phthalimide is exclusively used as an intermediate in the production of

- agricultural pesticides
- pigments and dyes
- pharmaceuticals and
- rubber processing chemicals

The only producer of isolated phthalimide in Germany manufactures and processes phthalimide in closed systems. The exhausts from manufacturing and processing are connected to particulate filters and air washing units. Virtually no phthalimide is emitted into the atmosphere. Waste from the manufacturing process is incinerated in incinerators for hazardous wastes. The wastewater from manufacturing and processing is led to a producer-owned industrial wastewater treatment plant at each site. Neither phthalimide nor its hydrolysis product phthalic acid were detected in the effluents of the wastewater treatment plants. To protect workers from exposure, several precautionary and protective measures are taken, e.g. during sampling, repair and maintenance. In the Sponsor country (Japan), similar measures are applied to protect the environment and the workers (e.g. phthalimide was not detectable in the effluents of the wastewater treatment plant of the production plant).

Phthalimide is an intermediate in dithalimfos (O,O-diethyl phthalimidophosphonothioate) and folpet (*N*-(trichloromethylthio)phthalimide) degradation but is shown to be rapidly degraded under environmental conditions.
A direct use of phthalimide is not known. Phthalimide is listed confidentially in the Danish and Finnish Product Registers in 2001 (last year of record). It is not listed in the Swedish and Norwegian Product Registers. The main use category is “use in closed system”. The Swiss product register does not list a consumer product containing phthalimide. In Japan; phthalimide has not been detected in 151 agricultural products (limit of detection: 0.01 ppm). Exposure of consumers to phthalimide is considered to be negligible.

RECOMMENDATION AND RATIONALE FOR THE RECOMMENDATION AND NATURE OF FURTHER WORK RECOMMENDED

Human Health: The chemical possesses properties indicating a hazard for human health (some indications for reproductive toxicity at high doses). Based on data presented by the Sponsor country and by the main producer in Germany (relating to production by 2 producers in 2 countries which accounts for 44-56 % of global production and relating to the use pattern in several countries), exposure to humans is anticipated to be low, and therefore this chemical is currently of low priority for further work. Countries may desire to investigate any exposure scenarios that were not presented by the Sponsor country.

Environment: The chemical is currently of low priority for further work. The chemical possesses properties indicating a hazard for the environment (aquatic toxicity). These hazards do not warrant further work as they are related to acute toxicity which may become evident only at high exposure level. They should nevertheless be noted by chemical safety professionals and users.