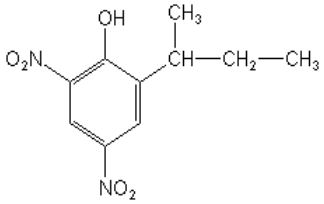
SIDS INITIAL ASSESSMENT PROFILE

CAS No.	88-85-7
Chemical Name	2-sec-butyl-4,6-dinitrophenol (Dinoseb)
Structural Formula	

SUMMARY CONCLUSIONS OF THE SIAR

Human Health

In young and adult female Fischer 344 rats, dermal absorption appeared to be biphasic. In six hours young and adult rats absorbed about 44% of the dose, while at 120 hours 75.9% was absorbed in young and 92.5% in adults. Adults excreted about 70% of the total recovered dose in urine, 16% in faeces and retained 7% in the body at 120 hours. HPLC analysis of urine collected at 24 hours from adults showed extensive metabolism of the parent compound. Blood had the highest concentration of 2-sec-butyl-4,6-dinitrophenol-derived radioactivity of the tissues examined.

In pregnant Swiss Webster mice, dosed by either intraperitoneal injection or gavage on gestation day 11, [^{14}C]-2-sec-butyl-4,6-dinitrophenol crossed the placenta and reached the embryo although a barrier to transfer was present as embryonic levels never exceeded 2.5% of maternal plasma levels. Peak embryonic levels of radioactivity were similar but reached much earlier after intraperitoneal than oral administration. In maternal animals, radioactivity reached all tissues. The elimination rate constant was 0.02/hr after gavage and 0.09/hr after intraperitoneal injection. Between 67 and 78% of the administered dose was recovered in urine and faeces within 64 hours of the administration of a single dose of the test substance, regardless of the route of administration.

The inhalation LC_{50} is 35-130 mg/m^3 for 4-hr exposure in rats, and laboured breathing and decreased activity were observed. The dermal LD_{50} is 40-146 mg/kg bw in rabbits, and decreased activity, salivation, nasal discharge, increased respiratory rate and ataxia were found. The oral LD_{50} is 5-50 mg/kg bw in rats, and prone position, bradypnea, diarrheal stool and decreased motor activity were noted.

No valid information is available concerning skin irritation. 2-sec-Butyl-4,6-dinitrophenol is highly irritating to the eye in rabbits. No information is available regarding sensitization.

In a combined repeated dose toxicity study with reproduction/developmental toxicity screening test, conducted according to OECD TG 422, Crj:CD(SD)IGS rats were given 2-sec-butyl-4,6-dinitrophenol by gavage at 0 (vehicle), 0.78, 2.33 or 7 mg/kg bw/day. Males were dosed for a total of 42 days from 14 days before mating, and females were dosed from 14 days before mating throughout the mating and pregnancy period to day 6 of lactation. In males, no deaths were observed in any of the groups. At 7 mg/kg bw/day, seven females died on gestation day 19 and one on gestation day 21 and one animal was moribund on each of gestation days 19 and 20. The LOAEL for males and NOAEL for females were 0.78 mg/kg bw/day, based on increases in hematocrit in males at 0.78 mg/kg bw/day and decreased extramedullary hematopoiesis of the spleen in females at 2.33 mg/kg bw/day.

In a developmental toxicity study conducted according to EPA guidelines, New Zealand White rabbits were dermally applied with 2-sec-butyl-4,6-dinitrophenol at 0, 1, 3, 9 or 18 mg/kg bw/day for six hours per day on gestation days 7 through 19. The NOEL for dermal toxicity was 1 mg/kg bw/day for females, based on maternal

mortality and hyperthermia.

2-sec-Butyl-4,6-dinitrophenol was not mutagenic in bacteria [OECD TG 471 and 472] and did not induce chromosomal aberrations in mammalian cells *in vitro* [OECD TG 473] either with or without metabolic activation.

Limited carcinogenicity studies are available in rats and mice. Based on the data available there is no indication of carcinogenic effect.

In above mentioned OECD TG 422 study in rats, sperm analysis in males at the end of the administration showed that there were no significant changes at 0.78 and 2.33 mg/kg bw/day in any of the sperm tests. At 7.0 mg/kg bw/day, motile sperm rate, progressive sperm rate, path velocity and viability rate were significantly increased, and the amplitude of lateral head displacement, abnormal sperm rate and abnormal tail rate were significantly decreased. In addition, the survivability rate and abnormal head rate tended to be higher without significant difference. At completion of the recovery period, there were no significant changes in any of the sperm tests at 0.78 and 2.33 mg/kg bw/day. At 7.0 mg/kg bw/day, the viability rate and survivability rate were significantly decreased and the abnormal sperm rate and abnormal head rate were significantly increased. In females, the gestation index was lowered at 7 mg/kg bw/day (8.3% compared with 100% in controls). No changes attributable to the chemical were noted in the number of estrous cases, copulation index, number of conceiving days, number of pregnant females, fertility index, gestation length, delivery or nursing conditions, number of corpora lutea, number of implantation sites or the implantation rate. In offspring, no changes attributable to the chemical were noted in the total number of births, number of stillbirths, number of live neonates, sex ratio, delivery index, birth index, live birth index, general condition, number of live neonates on day 4 and viability index on day 4, external anomalies, body weight and autopsy of offspring at 0.78 and 2.33 mg/kg bw/day. The NOEL for reproductive and developmental toxicity was 2.33 mg/kg bw/day based on sperm mortality and morphology in males and gestation index in females.

In a developmental toxicity study, DC rats were dosed by gavage 2-sec-butyl-4,6-dinitrophenol at 0, 2.5, 5, 10 or 15 mg/kg bw/day or were fed a diet containing this substance at 200 ppm (approximately 15 mg/kg bw/day) on gestation days 6 to 15. Maternal body weight gain was reduced at 10 and 15 mg/kg bw/day by gavage and 200 ppm by feeding. A significantly lowered weight and delayed ossification in fetuses at 15 mg/kg bw/day and increased incidence of fetuses with skeletal variations at 10 and 15 mg/kg bw/day were found after gavage. A significantly lowered fetal weight and increased incidence of fetuses with microphthalmia were noted after feeding. The NOAEL for maternal and developmental toxicity was 5 mg/kg bw/day based on decreased maternal body weight gain and fetal skeletal variations.

In an EPA guideline study, New Zealand White rabbits were dermally applied with 2-sec-butyl-4,6-dinitrophenol at 0, 1, 3, 9 or 18 mg/kg bw/day for six hours per day on gestation days 7 through 19. Maternal mortality and hyperthermia were found at 3 mg/kg bw/day and higher. The number of live fetuses was reduced at 9 mg/kg bw/day. Significantly increased incidences of fetuses with cleft palate, microcephaly, hydrocephaly, microphthalmia and anophthalmia were noted at 9 mg/kg bw/day. Hydrocephaly and anophthalmia were also present in the fetuses at 3 mg/kg bw/day. The NOEL for maternal and developmental toxicity was 1 mg/kg bw/day based on maternal mortality and hyperthermia and fetal hydrocephaly and anophthalmia.

Based on the studies described above, this chemical is a reproductive and developmental toxicant.

Environment

2-sec-Butyl-4,6-dinitrophenol is a solid at room temperature. Melting point, boiling point and vapour pressure are 40.6 °C, > 300 °C, 9.77×10^{-3} Pa (25 °C) respectively. Partition coefficient (Log P_{ow}) and water solubility are 3.57 (neutral form) and 34.5 mg/L at 20 °C respectively. Hydrolysis test according to TG111 shows no hydrolysis at pH4, pH7 and pH9 at 50 °C for 5 days. As the acid dissociation constant (pKa) is 4.47, 2-sec-butyl-4,6-dinitrophenol mainly exists in its dissociated form at environmentally relevant pH values. Indirect photo-oxidation by hydroxy radicals in the atmosphere is predicted to occur with a half-life of 31.82 hours. Half-lives of 22 h and >30 h for direct photolysis in aqueous solution are calculated based on measured first order rate constant for the neutral and dissociated species respectively. 2-sec-butyl-4,6-dinitrophenol is not readily biodegradable under aerobic conditions (BOD = 0 %). 2-sec-Butyl-4,6-dinitrophenol does not have a bioaccumulation potential based on the results of bioaccumulation tests (BCF: <0.3 - 1.0 at exposure level of 10 µg/l, <2.5 at exposure level of 1.0 µg/l). Fugacity modelling is based on the assumption that the substance is present in its neutral form in the aqueous compartments. Fugacity Model Mackay level III calculations indicate that 2-sec-butyl-4,6-dinitrophenol

will be distributed mainly to soil (59.8 %), air (29.9 %) and water (9.51 %) compartments if released to air. If released to water, 2-sec-butyl-4,6-dinitrophenol will distribute mainly to water (91.6 %) and sediment (7.8 %). If released to soil, 2-sec-butyl-4,6-dinitrophenol will be distributed almost exclusively to the soil compartment (99.6 %). If released simultaneously to air, soil and water, 2-sec-butyl-4,6-dinitrophenol will be distributed mainly to soil (79.8 %) and water (17.4 %) compartment. Henry's Law constant is 4.43×10^{-6} atm.m^3/mole at 20 °C.

Acute toxicities of 2-sec-butyl-4,6-dinitrophenol to aquatic organisms available from reliable tests are:

Fish (8 species)	48 h or 96 h -LC_{50}	= 0.032 - 0.54 mg/L
Daphnids (*Daphnia magna*)	48 h EC_{50}	= 0.24- 0.74 mg/L
Invertebrate (Scud)	96 h- $L(E)C_{50}$	= 1.8 mg/L

Algae (*Pseudokirchneriella subcapitata*) 72 h E_rC_{50} = 0.49-1.4 mg/L, 72 h E_bC_{50} = 0.81 mg/L

The chronic toxicities aquatic organisms are:

Lake trout	NOEC (fry weight)	< 0.0005	mg/L
Fathead minnow	NOEC (fry weight, mortality)	= 0.0145	mg/L
Daphnids (*Daphnia magna*),	21-d EC50 (reproduction)	= 0.17	mg/L
	21-d NOEC (reproduction)	= 0.062	mg/L.

Algae(*Pseudokirchneriella subcapitata*) NOECb (72h) = 0.19 mg/L , NOECr (72h) = 0.36 mg/L.

The terrestrial toxicities to higher plants and birds are shown in below. However results from efficacy field trials are difficult to interpret for the assessment of the toxicity of 2-sec-butyl-4,6-dinitrophenol to crop and target species because the exposure concentrations in the soil cannot be reliably determined from treatments expressed in units of kg/ha:

Higher plants (3 spp.) emergence after a 24hr aqueous exposure	EC_{50}	= 3.1-4.0 mg/L
Higher plants(7 crop spp)	10-18 d-EC_{50}	= 3.8 - 25 kg/ha (at high temperature)
	10-18 d-EC_{50}	= 9.1 - 43 kg/ha (at low temperature)
Higher plant (4 target spp)	42 d EC_{50}	< 0.56 - 1.12 kg/ha
Higher plants (3 spp.)	the inhibition rates of 0 to 53 %	= 0.01 – 0.06 kg/ha.
Birds (3spp.) dietary acute	8 d LC_{50}	= 410 - >540 ppm.

Exposure

The volume of 2-sec-butyl-4,6-dinitrophenol imported into Japan were estimated at 215 tons in 2004 and 110 tons in 2005. No 2-sec-butyl-4,6-dinitrophenol seems to be produced in Japan. In Japan, 2-sec-butyl-4,6-dinitrophenol is used as a polymerization inhibitor. This chemical was used as a pesticide in the past, but this use is not allowed now in the sponsor country. Although the pesticide use is not allowed in many OECD member countries for long time, the residue of 2-sec-butyl-4,6-dinitrophenol in the environment might remain as this chemical is not readily biodegradable. No consumer use is known for 2-sec-butyl-4,6-dinitrophenol.

According to the Japanese PRTR (Pollutant Release and Transfer Register) system, the released amount to the environment or transferred amount to off site of 2-sec-butyl-4,6-dinitrophenol should be reported to the authority. However, there were no reported releases or transfers of 2-sec-butyl-4,6-dinitrophenol from users or manufactures in Japan in 2002, 2003 and 2004. Use of 2-sec-butyl-4,6-dinitrophenol as a polymerization inhibitor may result in its release to the environment through waste water streams. However, 2-sec-butyl-4,6-dinitrophenol is processed in a closed system. According to these information, it is concluded that significant environmental exposure of this chemical is not expected in the sponsor country.

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

Human Health: The chemical is currently of low priority for further work. The chemical possesses hazards for human health (acute toxicity, irritation, repeated dose toxicity, reproductive and developmental toxicity). Based on data presented by the Sponsor country (relating to use and no production in the Sponsor country, global production is unknown) and relating to the use pattern in the Sponsor country, exposure to humans is anticipated to be low. Countries may desire to investigate any exposure scenarios that were not presented by the Sponsor country.

Environment: The chemical is a candidate for further work. The chemical possesses properties indicating a hazard to the environment (acute toxicity in the environment, chronic toxicity in fish and daphnids, acute toxicity in terrestrial higher plant, not readily biodegradable). Therefore, member countries are invited to perform an exposure assessment, a terrestrial (invertebrates e.g. earth worm) hazard assessment and, if necessary, a risk assessment for the environment.