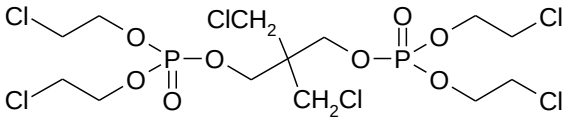
SIDS INITIAL ASSESSMENT PROFILE

CAS No.	38051-10-4
Chemical Name	2,2-BIS(CHLOROMETHYL)TRIMETHYLENE BIS(BIS(2-CHLOROETHYL)PHOSPHATE) (V6)
Structural Formula	

SUMMARY CONCLUSIONS OF THE SIAR

Physical-Chemical Properties

2,2-Bis(chloromethyl)trimethylene bis(bis(2-chloroethyl)phosphate (hereafter referred to as V6[1]) is a liquid at room temperature, with a freezing point of less than -50.5 ˚C and a boiling point of 252˚C. V6 has a relative density of 1.473 at 20˚C and a water solubility value of 232 mg/l at 20 °C. All of the above values are measured. The value for vapour pressure was estimated at 2.75 x 10^{-06} Pa at 25 °C. The log k_{ow} is 2.83 at 20^0C. It is of low volatility (estimated vapour pressure 2.75×10^{-6} Pa at 25°C

Human Health

The distribution and kinetics of [^{14}C]-V6 in male and female rats was investigated in accordance with OECD Guideline 417 and to GLP. Following oral administration of ^{14}C labelled V6 in the rat, the bioavailability was ≥ 100% at the low dose (15 mg/kg bw) and approximately 50% at the high dose (600 mg/kg bw), which was judged to be an underestimate due to the methodology used. V6 was completely absorbed from the gastrointestinal tract and blood kinetics varied between males and females at 15 mg/kg bw. Elimination half-life was 99 – 113 hours, irrespective of dose, route or sex and excretion was via the biliary route (60 %), urine (20 %) and a small amount exhaled as $^{14}CO_2$. [^{14}C]-V6 or its metabolites were distributed all over the body, but no target organs other then the organs of elimination were identified and major metabolites were found in the faeces. Limited information is provided for distribution and kinetics following intravenous administration, however it is of note that the elimination half lives for oral and i.v. routes are comparable, with differences observed in AUC and bioavailability are most likely due to differences in metabolism. An *in vitro* study conducted to GLP and to OECD Guideline 428, using human skin membranes as a model for dermal absorption, determined that the delivery of undiluted V6 and V6 in ethanol (0.2mg/cm^2) was 0.51 % and 6 %, respectively.

V6 is not acutely toxic, with an LD_{50} (rat) greater than 2000 mg/kg bw for both the oral and dermal routes of exposure. For inhalational exposure in a test carried out to OECD Guideline 403 (1981), the LC_{50} (rat) was greater than 1.65 mg/l which was the highest attainable aerosol concentration. Serum cholinesterase was significantly decreased in rats of both sexes following oral administration; however this was determined not toxicologically relevant in accordance with the WHO/FAO joint meeting of experts in pesticides residues. Serum cholinesterase activity was unaffected following dermal administration and brain cholinesterase activity was unaffected following oral and dermal administration.

Skin and eye irritation studies indicate that V6 is neither irritant nor corrosive following a single exposure in the

[1] V6 is a trade name of 2,2-Bis(chloromethyl)trimethylene bis(bis(2-chloroethyl)phosphate containing up to 7.5% w/w of the impurity tris(2-chloroethyl) phosphate (TCEP). Purer forms of the substance are marketed under separate trade names (TL10 and V66).

rabbit, and any mild effects were fully reversible. Data on respiratory irritation are not available.

V6 does not possess significant skin sensitisation potential in the guinea pig maximisation test carried out to OECD Guideline 406 (1992). Data on respiratory sensitisation are not available.

From a 28-day repeat dose toxicity study carried out in accordance with OECD Guideline 407 (1995), in which V6 was administered via oral gavage in rats, a NOAEL of 15 mg/kg bw/day was derived. This was based on an increase in relative and absolute liver weight and histopathological findings in the liver including hepatocellular hypertrophy and centrilobular hypertrophy in mid-dose (150 mg/kg bw/day) females and in high-dose (600 mg/kg bw/day) males and females. Other observations of note included significantly increased cholesterol levels and significant increases in absolute and relative thyroid weight in high dose males and females, and significantly increased prothrombin time in high-dose males. Data from a two-generation reproductive toxicity study (please refer to study detailed below) indicated similar findings; mid- (85.8 mg/kg bw/day) and high-dose (261.9 mg/kg bw/day) males and high-dose (302.3 mg/kg bw/day) females in the F0 generation had increased absolute and relative thyroid weight, accompanied by follicular hypertrophy and a reduction in colloid in males. High-dose males and females from both generations had increased absolute and relative liver weight, and in the F0 generation this was accompanied by hepatocyte hypertrophy. Based on this study, the NOAEL for parental toxicity in males is set at 29 mg/kg and for females at 97 mg/kg.

V6 did not induce gene mutation in bacterial assays with or without metabolic activation and did not induce an increase in the frequency of mutations in mouse lymphoma L5178Y cells, nor did it induce reproducible chromosomal aberration frequency in human lymphocytes in a test carried out to OECD Guideline 473 (1981). In an *in vivo* mouse micronucleus test conducted to OECD Guideline 474, V6 was not clastogenic. In conclusion, V6 is non-genotoxic *in vivo*.

Carcinogenicity data are not available for V6.

In an oral two-generation reproductive toxicity study conducted to OECD Guideline 416, V6 was administered to rats via the diet at doses of 29, 86 or 262 mg/kg bw/day for males and 33, 97 or 302 mg/kg bw/day for females. There were no effects on the male and female reproductive systems up to the highest doses tested and therefore the NOAEL derived for effects on fertility is approximately 262 and 302 mg/kg bw/day for males and females, respectively. Corpora lutea were not counted at scheduled sacrifice, which represented a deviation from the guideline. There was an increased number of runts on post-natal day one in mid- and high-dose groups of both generations, which may indicate toxicity to the offspring *in utero* and a decrease in pup weights in mid- and high-dose groups of both generations at certain time points. Other findings included decreased absolute spleen weight in high dose F0 pups and in all treated F1 pups, decreased relative spleen weight in high dose F1 pups, decreased absolute brain weight in all treated F1 pups, however relative weights were significantly increased. Absolute thymus weight of low and high dose F1 pups was also decreased, with no effect on the relative weights. A NOAEL of 29 mg/kg bw/day was derived for developmental toxicity based on the increased number of runts (defined as a pup with a weight less than the mean pup weight of the control group minus 2 standard deviations) and decreased pup weight at the mid- and high-doses. The low-dose of 29 mg/kg bw/day was considered the NOAEL for parental toxicity in males, based on thyroid weight changes and histopathology in mid- and high-dose groups for both generations and the mid-dose of 97 mg/kg bw/day was considered the NOAEL for parental toxicity in females based on liver and thyroid weight changes.

Environment

V6 has a moderately low adsorption coefficient (K_{oc} is 245, by read across of the log K_{oc} - log K_{ow} relationship from the structurally-related substance TDCP, for which a reliable adsorption study has been conducted). V6 has a low potential to bioaccumulate in fish (estimated BCF = 50.8).

Fugacity modelling shows that if released to air, most V6 would be precipitated to soil (>93%) and some would pass to water (7%). If released to water, almost all will remain in water (>99%). If applied to soil, most would remain in soil (>93%) though some would migrate to water (7%). There is relatively little movement of V6 between soil and water, because transfer via the air compartment is very slow.

V6 is not readily biodegradable, showing 5% degradation over 28 days. Evidence of partial degradation was seen in a study of inherent biodegradability, though the test method did not allow for a period of adaptation. While phosphate esters are known to be chemically susceptible to hydrolysis, V6 is expected to have a half-life of at least one year under environmental conditions, based on a standard preliminary hydrolysis test. It is expected to degrade in the atmosphere by reaction with hydroxyl radicals and a half-life of 5.0 hours has been estimated (rate constant = 77.2926×10^{-12} cm^3/molecule.sec).

Valid measured toxicity data are available for three aquatic taxonomic groups. The lowest effect values in short-term tests are a 96-h LC_{50} of 52 mg/l for Rainbow trout (*Oncorhynchus mykiss*), a 48-hour EC_{50} of 42 mg/l for the invertebrate *Daphnia magna*, and a 72-hour ErC_{50} and E_bC_{50} of 35 mg/l and 21 mg/l respectively for the alga *Pseudokirchneriella subcapitata*.

Two chronic test results are also available: the 21-day NOEC for *D. magna* reproduction is $\geq$ 3.68 mg/l and the 72-hour NOEC for *P. subcapitata* is 10 mg/l. A $PNEC_{aquatic}$ of 0.0736 mg/l has been derived by dividing the *D. magna* NOEC by an assessment factor of 50. There are no data for sediment-dwelling organisms.

A NOEC of 1,000 mg/l was obtained for wastewater treatment plant (WWTP) micro-organisms (activated sludge).

Data are also available for terrestrial organisms. A 14-day LC_{50} of > 1,000 mg/kg soil dry weight was determined for the earthworm *Eisenia foetida* (no effects were observed). When corrected for organic carbon content in the test medium, a 'standardised' result of > 340 mg/kg soil dry weight can be derived for risk assessment purposes. Reliable long-term studies have been conducted for the structurally-related substances TCPP and TDCP, and read-across of the results to V6 may be justified.

Exposure

Less than 5,000 tonnes were produced within the EU in 2000, at a single location (UK). EU consumption of V6 is less than 2,500 tonnes per year, and the EU is a net exporter of finished goods containing V6.

V6 is used as an additive flame retardant mostly (over 95%) in flexible polyurethane foams. It is physically combined with the material being treated rather than chemically combined. The amount of flame retardant used in any given application depends on a number of factors such as the flame retardancy required for a given product, the effectiveness of the flame retardant and synergist within a given polymer system, the physical characteristics of the end product and the use to which the end product will be put. V6 may be exported in its raw format or may be used in the manufacture of polyurethane (PUR) foam for use mainly in the automotive industry, with some used in furniture. Additionally, a small number of company-specific, low-tonnage minor uses have been identified. These are not described due to commercial sensitivity.

Occupational exposure to V6 may occur during its manufacture, during the manufacture and cutting of PUR foam and during the production of rebonded and loose crumb foam. Inhalation of vapours and skin contact are the predominant routes of exposure. Oral exposure is not considered to be a significant route of exposure. Exposure of workers to V6 via the inhalation and dermal routes does not present concern due to the presence of adequate controls, such as local exhaust ventilation and use of personal protective equipment..

Consumers do not come into direct contact with PUR foams. The foam is only used in ways in which it is enclosed and therefore it is concluded that exposure to consumers is negligible.

Emissions to the environment can occur to the atmosphere (by evaporation) and waste water. Sources of release include sites undertaking V6 production; manufacture of flexible foams; foam recycling ('rebonding' and 'loose-crumb'); and processing sites associated with the minor uses. Emissions to the environment could also occur from finished articles during their use and at disposal, via both evaporation and generation of small particles, due to weathering and wear. Leaching from landfill sites is considered possible, based on the physicochemical properties of V6, although input to the environment via this route is considered to be negligible for the EU risk assessment.

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 properties indicating a hazard for human health (repeated dose toxicity and developmental toxicity). However, based on data presented by the Sponsor country, the exposure situation at the workplace is controlled and adequate risk management measures are in place. Individual countries may wish to carry out their own exposure assessments, relevant for their own scenarios followed by a risk assessment.

Environment

The chemical is of low priority for further work because of its low hazard profile.

Note: V6 is one of four closely-related chlorinated alkyl phosphate ester flame retardants, all of which have undergone risk assessment in the EU. The other substances are: TDCP, CAS no. 13674-87-8; TCPP, CAS no. 13674-84-5; TCEP, CAS no. 115-96-8.The identified uses of V6 do not lead to a concern for the environment in the EU. The human health risk assessment is still being conducted.