Long chain Ca phenol derivatives: Human health tier III assessment

Chemical Name on the Inventory	CAS Number
Phenol, dodecyl-, sulfurized, carbonates, calcium salts	68784-25-8
Phenol, dodecyl-, sulfurized, carbonates, calcium salts, overbased	68784-26-9
Phenol, dodecyl-, sulfurized, calcium salts	68855-45-8
Phenol, tetrapropylene-, sulfurized, calcium salts	122384-85-4
Phenol, tetrapropylene-, sulfurized, carbonates, calcium salts	122384-86-5
Phenol, tetrapropylene-, sulfurized, carbonates, calcium salts, overbased	122384-87-6

Preface

This assessment was carried out by staff of the National Industrial Chemicals Notification and Assessment Scheme (NICNAS) using the Inventory Multi-tiered Assessment and Prioritisation (IMAP) framework.

The IMAP framework addresses the human health and environmental impacts of previously unassessed industrial chemicals listed on the Australian Inventory of Chemical Substances (the Inventory).

The framework was developed with significant input from stakeholders and provides a more rapid, flexible and transparent approach for the assessment of chemicals listed on the Inventory.

Stage One of the implementation of this framework, which lasted four years from 1 July 2012, examined 3000 chemicals meeting characteristics identified by stakeholders as needing priority assessment. This included chemicals for which NICNAS already held exposure information, chemicals identified as a concern or for which regulatory action had been taken overseas, and chemicals detected in international studies analysing chemicals present in babies' umbilical cord blood.

Stage Two of IMAP began in July 2016. We are continuing to assess chemicals on the Inventory, including chemicals identified as a concern for which action has been taken overseas and chemicals that can be rapidly identified and assessed by using Stage One information. We are also continuing to publish information for chemicals on the Inventory that pose a low risk to human health or the environment or both. This work provides efficiencies and enables us to identify higher risk chemicals requiring assessment.

The IMAP framework is a science and risk-based model designed to align the assessment effort with the human health and environmental impacts of chemicals. It has three tiers of assessment, with the assessment effort increasing with each tier. The Tier I assessment is a high throughput approach using tabulated electronic data. The Tier II assessment is an evaluation of risk on a substance-by-substance or chemical category-by-category basis. Tier III assessments are conducted to address specific concerns that could not be resolved during the Tier II assessment.

These assessments are carried out by staff employed by the Australian Government Department of Health and the Australian Government Department of the Environment and Energy. The human health and environment risk assessments are conducted and published separately, using information available at the time, and may be undertaken at different tiers.

This chemical or group of chemicals are being assessed at Tier III because the Tier II assessment indicated that it needed further investigation. The report should be read in conjunction with the Tier II assessment.

For more detail on this program please visit: www.nicnas.gov.au

Acronyms & Abbreviations

Synopsis

Under the Inventory Multi-tiered Assessment and Prioritisation (IMAP) Framework, it was determined that further work was required to fully assess the reproductive toxicity data available for the chemicals in this group and to determine the concentration limit of tetrapropenyl phenol (TPP) that should lead to hazard classification for the chemicals in this group.

The chemicals in this group are substances of unknown or variable composition, or of biological origin (UVCB). The chemical TPP and the calcium salt of TPP (CaTPP) are intermediates in the manufacture of these chemicals, and may remain as impurities in small concentrations. The potential for these chemicals to cause reproductive toxicity relates to the presence of residual TPP.

Using available data for reproductive toxicity of chemicals containing residual TPP, as well as supporting data from reproductive toxicity studies conducted with TPP, this assessment aimed to review whether the classification: ‘Category 3 substances toxic to reproduction’—with the risk phrase ‘Possible risk of impaired fertility’ (Xn; R62) in the Hazardous Substances Information System (HSIS) (Safe Work Australia) in the presence of 0.5 % TPP, would be sufficient to protect the health and safety of the general public and workers using these chemicals in industrial settings.

Based on this assessment, it was concluded that there is clear evidence from experimental animal studies that TPP can adversely affect reproduction, and that the adverse effects on reproduction are not secondary to systemic toxicity. These studies also provide mechanistic evidence of possible modification of androgen and oestrogen receptor-mediated signalling. The critical impurities, TPP and CaTPP, are not included on the Inventory and classification of these chemicals in Australia is not considered warranted. However, for purposes of assessment of the chemicals in this group, the available data indicate that an appropriate outcome would be reached by considering these impurities (TPP and CaTPP) to be Category 2 substances toxic to reproduction (Approved Criteria). The weight of evidence from the available studies supports the notion that the reproductive toxicity associated with chemicals containing residual TPP is primarily attributable to the TPP. Therefore, according to the current Approved Criteria [NOHSC:1008(2004)], it is concluded that the advisory classification is sufficient and that the chemicals in this group should remain classified as ‘Category 3 substances toxic to reproduction’—with the risk phrase ‘Possible risk of impaired fertility’ (Xn; R62), with a concentration limit of 0.5 % for TPP/CaTPP (applicable for substances classified as Category 2 toxic to reproduction (fertility) present in mixtures). The available studies indicate that the resulting concentration limit of 0.5 % is sufficient to protect humans from adverse fertility effects from the chemicals in this group.

The Tier II assessment report for the chemicals in this group is available at: http://www.nicnas.gov.au/chemical-information/imap-assessments/imap-group-assessment-report?assessment_id=130 and contains detailed assessment information that remains valid (NICNAS). New or updated information is included in the Tier III human health report, in the relevant sections. The Tier II and Tier III reports for this chemical should be read together.

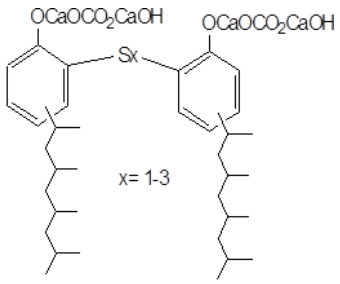
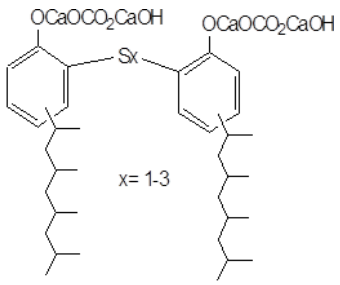
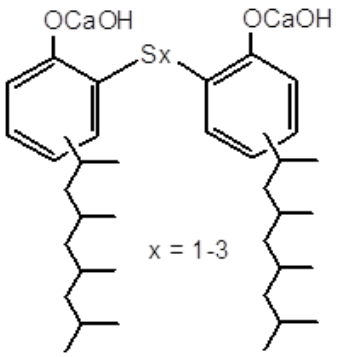
Rationale for Tier III Assessment

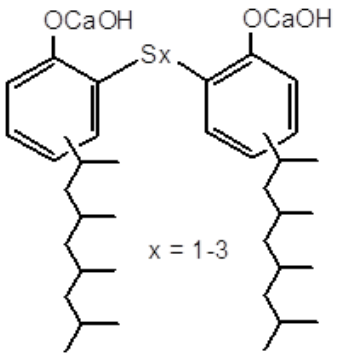
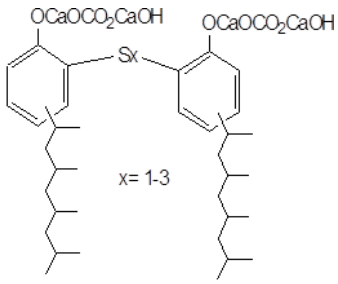
Based on the IMAP Tier II Health Hazard assessment, the UVCBs in this group were assessed to have reproductive toxicity due to unreacted TPP/CaTPP. Risk characterisation of these chemicals is ultimately dependent on the percentage of TPP/CaTPP impurity remaining in the finished product. The Tier II assessment recommended that further work be conducted to fully assess the reproductive toxicity data of the chemicals in this group. However, an advisory recommendation was made to classify these chemicals containing ≥0.5 % unreacted TPP/CaTPP as Category 3 substances toxic to reproduction with the risk phrase ‘Possible risk of impaired fertility’ (Xn; R62) under the current Approved Criteria and the equivalent classification (‘Suspected of damaging fertility’(Cat 2; H361f)) under the adopted Globally Harmonised System of Classification and Labelling of

Chemicals (GHS). This was based on the assumption that the impurities, TPP and CaTPP, could be considered Category 2 reproductive toxins with the relevant standard cut-off concentrations under the Approved Criteria.

In 2014, the European Chemicals Agency (ECHA) Risk Assessment Committee (RAC) adopted an opinion recommending that TPP be classified as Toxic to Reproduction 1B (H360F) with a Generic Concentration Limit (GCL) of 0.3 % (ECHA RAC, 2014). If the ECHA RAC opinion is applied, this would indicate that the chemicals in this group should be considered as reproductive toxicants at 0.3 % TPP/CaTPP. This potential change in the cut-off concentration is not health-based, but is a result of the different general cut-offs under GHS and the Approved Criteria. As the chemical impurities TPP and CaTPP are not listed on the Inventory, this Tier III assessment was conducted to determine whether the advisory recommendation for classification of the chemicals in this group should be modified to reflect the lower concentration arising from the GHS classification of TPP. This assessment only applies to the UVCB chemicals in this group and does not constitute full assessment of TPP or CaTPP.

Chemical Identity

Chemical name on the Inventory	CAS Number	Structural Formula	Molecular Formula	Molecular Weight
Phenol, dodecyl-, sulfurized, carbonates, calcium salts	68784-25-8		Unspecified	667.1 (S=1) to 731.2 (S=3)
Phenol, dodecyl-, sulfurized, carbonates, calcium salts, overbased	68784-26-9		Unspecified	667.1 (S=1) to 731.2 (S=3)
Phenol, dodecyl-, sulfurized, calcium salts	68855-45-8		Unspecified	667.1 (S=1) to 731.2 (S=3)

Chemical name on the Inventory	CAS Number	Structural Formula	Molecular Formula	Molecular Weight
Phenol, tetrapropylene-, sulfurized, calcium salts	122384-85-4		Unspecified	667.1 (S=1) to 731.2 (S=3)
Phenol, tetrapropylene-, sulfurized, carbonates, calcium salts	122384-86-5		Unspecified	667.1 (S=1) to 731.2 (S=3)
Phenol, tetrapropylene-, sulfurized, carbonates, calcium salts, overbased	122384-87-6	No Structure Available	Unspecified	667.1 (S=1) to 731.2 (S=3)

Health Hazard Information

The reproductive toxicity of the chemicals in this group correlates with residual amount of unreacted TPP/CaTPP present as an impurity. Manufacturers can reduce the concentration of unreacted TPP in the mixtures to levels that do not cause reproductive toxicity in experimental studies. Therefore, the reproductive toxicity data from studies analysing mixtures containing TPP as an impurity will be used to determine the concentration level that would be considered safe for reproductive health. In addition, the data from studies analysing the reproductive toxicity of the chemical TPP, will be used to support the data from mixtures.

Reproductive and Developmental Toxicity

Studies with UVCB substances containing TPP as an impurity

In a two-generation reproductive toxicity study conducted according to the Organisation for Economic Co-operation and Development (OECD) Test Guideline (TG) 416 (two-generation reproduction toxicity), a chemical in this group (phenol, dodecyl-, sulfurized, carbonates, calcium salts, overbased; CAS No. 68784-26-9) was administered to Sprague Dawley (SD) rats (30 animals/sex/group) at doses of 0, 50, 300 or 1000 mg/kg bw/day, by oral gavage for at least 71 days prior to mating and throughout breeding, gestation and lactation until necropsy. The test substance was calculated to contain approximately 6.7 % residual TPP (the converted dose administered was equivalent to 0, 3.4, 20.1 or 67 mg TPP/kg bw/day, respectively). The offspring were exposed to the test substance in utero, during lactation and post-weaning for at least 77 days (first generation of offspring (F1)) or 88 days (F1 satellite cross-breeding phase). Reduced body weight gain, increased pituitary and liver weight, and decreased testicular, epididymides and ovary weights were observed at 1000 mg/kg bw/day. Reduced body weight gain and increased pituitary weights (only in parental (F0) males) were also observed at 300 mg/kg bw/day. Reproductive performance was affected at 1000 mg/kg bw/day, as indicated by reduced fertility indices, difficult labour

and reduced live litter size. Results from the satellite cross-breeding phase suggested that these effects were more severe in the females compared with the males. On the basis of these findings, NOAELs of 50 mg/kg bw/day (equivalent to 3.4 mg TPP/kg bw/day) and 300 mg/kg bw/day (equivalent to 20.1 mg TPP/kg bw/day) were established for systemic and reproductive toxicity, respectively (Nemec et al., 1995).

In a two-generation reproductive toxicity study conducted according to the OECD TG 416, the test substance EC No. 415-930-6 (reaction mass of: Ca salicylates (branched C10-14 and C18- 30 alkylated); Ca phenates (branched C10-14 and C18-30 alkylated); Ca sulfurised phenates (branched C10-14 and C18-30 alkylated); no CAS No. available) was administered to SD rats (28 animals/sex/group) at doses of 0, 50, 250 or 1000 mg/kg bw/day, daily by oral gavage for at least 10 weeks prior to mating and throughout breeding, gestation and lactation until necropsy. The test substance contains approximately 3.8 % residual TPP (the converted dose administered was equivalent to 0, 1.9, 9.5 or 38 mg TPP/kg bw/day, respectively). The F1 (first generation) animals were dosed through post-weaning maturation, mating, gestation and lactation for at least 12 weeks. Reduced body weight was observed in the males of the F0 (parental generation) and F1 generations at 1000 mg/kg bw/day, but not in the females. A non-dose-related increase in failure to achieve pregnancy was observed in the F0 animals at all doses and in the F1 animals at 1000 mg/kg bw/day. Due to the absence of this effect in the F1 animals at 50 and 250 mg/kg bw/day, the authors interpreted the effects on fertility to be present at 1000 mg/kg bw/day only. A NOAEL of 250 mg/kg bw/day (equivalent to 9.5 mg TPP/kg bw/day) was established for reproductive toxicity in this study (Wood et al., 2002).

In a two-generation reproductive toxicity study conducted according to OECD TG 416, the test substance EC No. 430-180-1 (reaction mass of: calcium bis(C10- 14 branched alkyl salicylate); calcium bis(C18-30-alkyl salicylate); calcium C10-14 branched alkylsalicylato-C18-30- alkyl salicylate; calcium bis (C10- 14 branched alkyl phenolate); calcium bis (C18-30-alkyl phenolate); calcium C10-14 branched alkylphenolato-C18-30- alkyl phenolate; C10-14 branched alkyl phenol; C18-30-alkyl phenol; no CAS No. available) was administered to SD rats (28 animals/sex/group) at doses of 0, 5, 30 or 150 mg/kg bw/day, by oral gavage, for at least 10 weeks prior to mating and throughout breeding, gestation and lactation until necropsy. The test substance was reported to contain approximately 26 % TPP (the converted dose administered was equivalent to 0, 1.3, 7.8 or 39 mg TPP/kg bw/day, respectively). All F1 animals were dosed during post-weaning maturation, mating, gestation and lactation for at least 10 weeks. The treated males in the F0 and F1 generations had reduced seminal vesicle/coagulating gland tissue weights compared to the controls. However, no microscopic alterations and no adverse effects were associated with these weight changes. Therefore, an NOAEL of 150 mg/kg bw/day (equivalent to 39 mg TPP/kg bw/day) was established for reproductive toxicity in this study (Wood et al., 2003).

In a one-generation reproductive toxicity study conducted according to the OECD TG 415 (one-generation reproduction toxicity), the test substance EC No. 455-880-2 (reaction mass of: calcium bis(C10- 14 branched alkylsalicylate); calcium bis(C18-30 alkyl salicylate); calcium bis(C10-14 branched alkyl phenolate); calcium bis(C18-30 alkyl phenolate); lubricating oil (C15-30); no CAS No. available) was administered to SD rats (30 animals/sex/group) at doses of 0, 50, 170 or 500 mg/kg bw/day by oral gavage for 70 consecutive days prior to mating. The males were dosed through the period of mating until necropsy for up to a total period of 133–139 days, whilst the females were dosed through mating, gestation and lactation day 21 for up to a total period of 128–133 days. The test substance was calculated to contain approximately 2.5 % TPP (the converted dose administered was equivalent to 0, 1.25, 4.25 or 12.5 mg TPP/kg bw/day, respectively). No adverse effect on reproduction was observed in this study; therefore, an NOAEL of 500 mg/kg bw/day (equivalent to 12.5 mg TPP/kg bw/day) was established for reproductive toxicity (Knapp et al., 2008).

In a well-conducted reproductive and developmental toxicity study, following OECD TG 422 (combined repeated dose toxicity study with the reproduction/developmental toxicity screening test), the test substance (phenol, tetrapropylene-, sulfurized, calcium salts; CAS No. 122384-85-4) was administered to SD rats via oral gavage, to 12 animals/sex/dose for generation F0, at dose levels of 0, 50, 300 and 1000 mg/kg bw/day. The test substance was an approximate blend of 54 % alkyl phenate sulfide oligomers, 43 % highly refined lubricant base oil and 3 % (30 mg/kg bw/day in the highest dose group) unreacted TPP and CaTPP. Groups of F0 males were dosed daily from four weeks prior to mating period, which continued during and post mating for a total of 70 days. Groups of F0 females were dosed daily from four weeks prior to mating period, continuing during and post mating, gestation and through to day four of lactation. There were no effects reported at any dose level on fertility, mean live litter size, mean testes or ovary weights or sperm counts, although there was a slight decrease in mean body weight at the highest dose level. The reproductive toxicity NOAEL was reported as 1000 mg/kg bw/day for male and female rats (OECD, 2009).

In a one-generation oral study (Edward et al., 2012), conducted according to OECD TG 415, an analogue described as 43 % alkyl phenate sulfide oligomer, 50 % highly-refined lubricant based oil and 0.1-0.2 % wt free unreacted TPP was administered, via oral gavage, to 30 animals/sex/dose to Crl:CD(SD) rats (F0). Both sexes were dosed daily with concentrations of 0, 250, 500 or 1000 mg/kg bw/day for approximately 70 consecutive days prior to mating. Males were dosed daily and euthanised after 84 treatments. Female rats were dosed throughout mating, gestation, lactation and until euthanised after 127 treatments. There were no effects reported at any dose level on fertility, mean testes or ovary weights, mean live litter size and no microscopic findings in the F0 or F1 males and females after scheduled necropsy. The reproductive toxicity NOAEL was reported as >1000 mg/kg bw/day for male and female rats. In the absence of neonatal toxicity at all dose levels, a NOAEL for neonatal toxicity was reported as >1000 mg/kg bw/day. This study emphasised the importance of the amount of unreacted TPP or CaTPP as the causative agent for the adverse reproductive effects seen with some commercial blends.

Reproductive toxicity studies with TPP

In a two-generation reproductive toxicity study conducted according to OECD TG 416, TPP was administered to SD rats (30 animals/sex/group) in the diet at doses of 0, 1, 1.5, 15 or 75 mg/kg bw/day. F0 animals were administered the chemical for 129–134 consecutive days, and F1 animals were administered the chemical for 210–227 consecutive days. Due to reduced fertility in all groups (including control) in the F1 animals, they were re-bred to produce two second generation (F2) litters, the F2 and the F2a litters. Significant reductions in body weights were observed in the F0 and F1 animals at 75 mg/kg bw/day. Significant reductions in the number of pups born and live litter sizes were observed in the F2a litters at 75 mg/kg bw/day. The mean number of implantation sites was significantly reduced in the F0 females. Due to multiple gestations (F2 and F2a litters), the implantation was not determined in F1 females. In the F0 and F1 adult females, significantly lengthened oestrous cycles, increased number of females in persistent dioestrus, as well as reductions in ovary weights and the number of corpora lutea were observed at 75 mg/kg bw/day. Vaginal patency also occurred earlier in the F1 offspring at 75 mg/kg bw/day. The degree of maternal toxicity (significant reductions in body weights in the F0 and F1 animals) at 75 mg/kg bw/day was insufficient to account for the female fertility effects observed. In the F0 and F1 adult males, significant reductions in the weights of accessory reproductive organs, including epididymis, prostate, seminal vesicle and coagulating gland and lower mean epididymal sperm concentration

were observed at 75 mg/kg bw/day. Testicular weights were also lower in the F1 adult males at 75 mg/kg bw/day. The only histopathological finding attributed to the chemical was renal mineralisation observed in the F0 males at 75 mg/kg bw/day and in the F1 males at 15 and 75 mg/kg bw/day. Based on the observations, an NOAEL of 15 mg/kg bw/day was established for maternal toxicity, and a NOAEL of 15 mg/kg bw/day was established for reproductive toxicity (Edwards et al., 2012).

In a one-generation reproductive toxicity study conducted according to the OECD TG 415, TPP was administered to SD rats (30 animals/sex/group) at doses of 0, 5, 25 or 125 mg/kg bw/day, by oral gavage for 73 consecutive days prior to mating. Significant reductions in body weights were observed in the males at 25 and 125 mg/kg bw/day and in the females at 125 mg/kg bw/day. Significant reductions in the mean absolute liver weight were observed in the males at 125 mg/kg bw/day and in the females at 25 and 125 mg/kg bw/day. A significant increase in adrenal weights with hypertrophy of adrenal cortex was observed in the males at 125 mg/kg bw/day, and renal mineralisation was observed in the males at 25 and 125 mg/kg bw/day and in the females at 125 mg/kg bw/day. In the females, significant reductions in the mean absolute ovary weight were observed at 25 and 125 mg/kg bw/day. At 125 mg/kg bw/day, decreased corpora lutea and increases in ovarian cysts, endometrial gland cysts, the length of oestrous cycle, the number of animals in persistent oestrus or dioestrus, and the number of acyclic animals, were observed. The degree of maternal toxicity (significant reduction in body weights) at 125 mg/kg bw/day was insufficient to account for the female fertility effects observed. In the males, a significant reduction in the mean seminal vesicle/coagulating gland absolute weight was observed in all treatment groups. However, male accessory reproductive organ weights, including the seminal vesicle and prostate, are sensitive to body weight changes (Chapin et al., 1993; Rehm et al., 2008). Therefore, the statistically significant differences observed at 5 mg/kg bw/day were not considered to be toxicologically relevant as this was not observed in the two-generation reproductive toxicity study described previously. A significant reduction in the mean cauda epididymides absolute weight was observed at 25 and 125 mg/kg bw/day. Significant reductions in the mean weights of prostate, testes and epididymides and mean epididymal sperm concentration were observed at 125 mg/kg bw/day. Based on these findings, an NOAEL of 5 mg/kg bw/day was established for systemic toxicity and 5 mg/kg bw/day for reproductive toxicity (Knapp, 2006).

Related mechanistic studies

An in vitro rat prostate androgen receptor competitive binding assay was conducted in compliance with the Endocrine Disruptor Screening Program Test Guidelines OPPTS 890:1150. The ability of TPP to inhibit the binding of a radiolabelled ligand, 3H-R1881, to the androgen receptor, was evaluated. The cytosolic fraction from the pooled prostate of 30 castrated male SD rats was used in this study. The mean TPP response curve indicated that the chemical had the ability to disrupt ligand binding from an approximate concentration of 10 µM. Complete inhibition was observed at a concentration of 1 mM. On the basis of this assay, the chemical was considered to be an androgen receptor binder (Thomas et al., 2012a).

An in vitro rat uterine oestrogen receptor competitive binding assay was conducted in compliance with the Endocrine Disruptor Screening Program Test Guidelines OPPTS 890:1250. The ability of TPP to inhibit the binding of a radiolabelled ligand, hexatritiated 17ß-oestradiol, to the oestrogen receptor was examined. Cytosolic fraction from the pooled uterine tissue of 30 ovariectomised female SD rats was used in this study. The chemical disrupted ligand binding from approximately 10-7 M concentration and resulted in complete inhibition at a concentration of 10-5 M. The chemical was concluded to interact with the oestrogen receptor (Thomas et al., 2012b).

In two separate uterotrophic assays conducted according to OECD TG 440 (uterotrophic bioassay in rodents), TPP was similarly administered to ovariectomised female SD rats (six animals/group) at doses of 0, 75, 125, 250 or 500 mg/kg bw/day, for three consecutive days, by oral gavage. A positive control group received an oestrogenic positive control substance (17α-ethynylestradiol) and a vehicle control group received the vehicle only. Reductions in body weight gain and significant increases in the mean uterine weight were observed in all treatment groups except the vehicle control group in both studies. Both studies suggested that the chemical ‘demonstrated or mimicked biological activities consistent with agonism of natural oestrogens’ (Edwards et al., 2010a; Edwards et al., 2010b).

Four female pubertal assays were conducted in immature female SD rats (15 animals/group) by administering TPP once daily for 20 consecutive days (post-natal days 22–41) via gavage. Two studies were conducted with TPP at doses of 10, 50, 200 or 800 mg/kg bw/day, one study at 5, 20 or 60 mg/kg bw/day and another study at 60, 250 or 1000 mg/kg bw/day. The control groups in each study received the vehicle using a comparable regimen. The observations from these studies indicated that some oestrogenic effects of the chemical were observed at doses of 20 mg/kg bw/day and above, including early attainment of vaginal patency, oestrous cycle disturbances, reduced weights of the uterus, thymus and ovaries/oviducts, and morphological changes including absence of corpora lutea, oocyte degeneration and necrosis of follicular cells in the ovaries. Systemic toxicity was observed at 200 mg/kg bw/day (reduced body weight) and 800 mg/kg bw/day (mortality) (Knapp, 2007a; Knapp, 2007b; Knapp, 2009a; Knapp, 2009b).

Determination of concentration cut-off for TPP

For the chemicals in this group, the available data from chemicals containing TPP as an impurity, support the recommended classification of Category 3 substance toxic to reproduction—with the risk phrase ‘Possible risk of impaired fertility’ (Xn; R62) in the HSIS (Safe Work Australia). In addition, the weight of evidence from the studies using TPP, support the fact that the reproductive toxicity of these chemicals is mainly caused by the residual TPP.

The available in vivo study data and the supporting mechanistic data clearly identify that TPP is a probable reproductive toxin (fertility). The current Approved Criteria [NOHSC:1008(2004)] specify that ‘for classification of a substance into Category 2 for impaired fertility (may impair fertility), there should normally be clear evidence in one animal species, with supporting evidence on mechanism of action or site of action’. Clear evidence is available from reproductive studies in rats that TPP can adversely affect reproduction, and the adverse effects on reproduction are not considered to be secondary to systemic toxicity. In addition, mechanistic evidence indicates possible modification of androgen and oestrogen receptor-mediated signalling. Therefore, while these chemicals are not classified under HSIS, for the purpose of this assessment, it is assumed that the impurities, TPP and CaTPP, could be considered Category 2 reproductive toxins. Based on the current Approved Criteria [NOHSC:1008(2004)], a concentration limit of 0.5 % is applied for substances classifiable as Category 2 toxic to reproduction (fertility).

According to the HSIS Guidance Material for Hazard Classifications, concentration cut-off levels for chemicals are assigned in accordance with the Approved Criteria [NOHSC:1008(2004)] (Safe Work Australia). The guidance states that 'a mixture is classified as a hazardous substance if it contains at least one ingredient at a concentration equal to, or above, the lowest concentration cut-off level given for that ingredient' (Safe Work Australia). On the presumption that TPP should be considered a probable reproductive toxin (Category 2), the classification of the chemicals in this group is based on the 0.5 % cut-off level of TPP present. The available studies indicate that a concentration limit of 0.5 % is sufficient to protect humans from adverse fertility effects. In addition, the reduction of the concentration limit to 0.3 % would not be health based but rather a purely technical outcome of the different general cut-off value in GHS. Therefore, taking into consideration that TPP is not listed on the Inventory or HSIS, NICNAS recommends that the chemicals in this group containing ≥0.5 % residual TPP require classification for reproductive toxicity (refer to **Recommendations** section).

The current Approved Criteria [NOHSC:1008(2004)] specify that, under normal circumstances, it is considered that effects seen only at doses in excess of the limit dose (1000 mg/kg) would not necessarily lead to classification as 'Toxic to reproduction'. It was suggested by industry that this 'limit dose', combined with the NOAEL derived from reproductive studies on TPP, could be used to derive the concentration limit for TPP in these chemicals. However, this approach is considered unsuitable for the purposes of setting the concentration limit for this group of chemicals. Firstly, while the reproductive toxicity in these chemicals is considered to be due to the TPP impurity present in these chemicals, there are uncertainties around the toxicity profile of the other components in these UVCBs, especially for humans, as they have not been assessed in isolation. Therefore, the use of a generic 1000 mg/kg limit dose would not take this uncertainty in to account. In addition, direct use of an NOAEL dose derived from animal studies assumes that this dose, safe for animals, would also be safe for humans. This is incorrect and, for regulatory purposes, the risk assessment should take into account both inter- and intra-species differences.

NICNAS has, therefore, not used this approach to set a health-based limit. The available data from tests on chemicals in this group indicate that a health-based limit could be of the order of 2.5-3 % TPP. However, the available data are not sufficient to determine this value accurately. For this reason, NICNAS determined that the cut-off value arising from application of the Approved Criteria (0.5 %) would be the most appropriate value. While the case could be made using the generic cut-off concentration prescribed under GHS, the health-based data do not indicate that a more conservative position, with a lower cut-off, is necessary.

This determination applies only to chemicals in this group containing unreacted TPP. Should other formulations containing TPP (or its calcium salt) be introduced in Australia, a separate assessment would be required.

NICNAS Recommendation

Based on this Tier III assessment, the classification recommendation made in the Tier II assessment: 'Category 3 substances toxic to reproduction' — with risk phrase 'Possible risk of impaired fertility' (Xn, R62) in the HSIS in the presence of ≥0.5 % TPP, is sufficient to protect the health and safety of the general public and workers using these chemicals. No further change is recommended.

Regulatory Control

Work Health and Safety

The chemical is recommended for classification and labelling under the current approved criteria and adopted GHS as below. This assessment does not consider classification of physical and environmental hazards.

Hazard	Approved Criteria (HSIS)[a]	GHS Classification
Reproductive and Developmental Toxicity	Repro. Cat 3 - Possible risk of impaired fertility (Xn; R62)*	May damage fertility (H360F)

[a] Approved Criteria for Classifying Hazardous Substances [NOHSC:1008(2004)].

[*] Existing Hazard Classification. No change recommended to this classification

Advice for consumers

Products containing the chemicals should be used according to the instructions on the label.

Advice for industry

The advice provided in the human health Tier II IMAP report remains unchanged.

A review of the physical hazards of the chemical has not been undertaken as part of this assessment.

References

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