ATC Response to NICNAS Recommendations on

Alkyl Phenate Sulfides

 ATC Document 114

 August 2013

Alkyl Phenate Sulfides

Thank you for the opportunity to comment on the Australian Government’s Inventory Multi-tiered Assessment and Prioritization (IMAP) for the category of chemicals identified as Long Chain CA Phenol derivatives (including CAS #s 68784-25-8, 68784-26-9, 68855-45-8, 122384-85-4, 122384-86-5, 122384-87-6). For the purposes of this public comment, this category of chemicals will be referred to as ‘alkyl phenate sulfides’.

The Technical Committee of Petroleum Additive Manufacturers in Europe (ATC) wishes to comment specifically to the NICNAS recommendation that the alkyl phenate sulfides considered in this IMAP assessment have hazards resulting in a classification of Reproduction Category 3 – Possible risk of impaired fertility (Xn; R62) using the Approved Criteria for Classifying Hazardous Substances [NOHSC:1008(2004)] or the equivalent GHS classification of Reproductive toxicity Category 2 (H361).

We respectfully request that NICNAS reconsider this recommendation and the way it is reflected in the HSIS. A comprehensive assessment of compositional, physical-chemical and toxicological data for this category of chemicals provides compelling evidence that adverse effects observed in repeated-dose reproduction toxicity assays are the direct result of the free residual unreacted levels of the known reproduction toxicant tetrapropenyl phenol (TPP; aka para-dodecylphenol) and not due to the alkyl phenate sulfide oligomers themselves. In animal studies, TPP has produced dose-responsive reproductive effects, ranging from mild reductions to male and female organ weights, to alterations in functional parameters such as estrous cyclicity, and reduced fertility. In contrast, the weight-of-evidence does not support a reproductive hazard due to the oligomeric alkyl phenate sulfide species themselves.

Therefore, this comment is to respectfully request that the Australian Government not assign a reproduction hazard classification to the listed alkyl phenate sulfides, but rather to allow the classification algorithm for preparations (mixtures) to drive the classification of alkyl phenate sulfides and formulated products containing them based upon the measured concentration of the known reproduction toxicant TPP.

This approach is more appropriate for alkyl phenate sulfides as it encourages manufacturers to reduce the levels of the known reproduction toxicant TPP to levels that do not result in a hazard classification for alkyl phenate sulfides and products containing them. The known TPP content of each commercial alkyl phenate sulfide and the application of the mixture rules has been the standard approach to classification and labelling by the global lubricant industry for the past eight years since reproductive effects of TPP became widely established. It is also recognized as the most valid approach to classification and labelling of substances containing impurities for reproductive toxicity by other respected regulatory authorities such as the European Chemicals Agency (see Guidance on the application of CLP criteria). This practice takes into consideration the presence of both unreacted free TPP and any unreacted calcium salts of this alkylphenol that may remain as impurities due to the manufacturing process for alkyl phenate sulfides. ATC has also met with the European Chemicals Agency and the Dutch Competent Authority to clarify that TPP is the causal agent responsible for the assessment of reprotoxicity for alkyl phenate sulfides that contain unreacted TPP. Additionally, the Australian government may wish to consider that a formal proposal for the harmonization of classification and labelling of TPP has been submitted to the European authorities, and their decision is expected during the first half of 2014.

Toxicokinetic considerations

As indicated in the NICNAS IMAP assessment, alkyl phenate sulfides are high molecular weight (>660 mw), poorly water soluble (0.2 mg/L) and highly lipophilic (logP > 8 ) oligomers of TPP bridged by sulfur atoms. This combination of physico-chemical properties is not conducive to absorption across the gastrointestinal tract upon oral administration. As indicated in the IMAP assessment, a significant amount of an administered oral dose of alkyl phenate sulfide would be expected to pass directly through the gastrointestinal tract and be eliminated in the feces unchanged. This observation is particularly important when one assesses the repeated-dose reproduction toxicity data available for commercial alkyl phenate sulfides. The toxicokinetic profile strongly indicates that adverse findings in reproduction toxicity studies is not due to alkyl phenate sulfide oligomers because of their very low bioavailability, but rather due to the known reproductive toxicant TPP which is typically present in commercial alkyl phenate sulfides at free unreacted concentrations ranging between 3 wt% - 14 wt% percent (OECD SIAR).

Repeated-dose reproduction toxicity studies

The IMAP assessment cites the results of a combined systemic and reproduction screening oral gavage toxicity study in rats (OECD 422) using a test material composed of 54 wt% alkyl phenate sulfide oligomers, 43 wt% highly refined lubricant base oil and 3 wt% TPP. The test material is identified by the CAS#s 122384-85-4 and 68855-45-8 which correspond to the same substance but using alternative nomenclature (i.e., tetrapropenyl phenol vs dodecylphenol). No adverse effects on fertility, mating and mean live litter size were observed in this study at the highest dose of alkyl phenate sulfide tested (1000 mg/kg/day; equivalent to 540 mg/kg/day alkyl phenate sulfide oligomer).

The second study cited is a 2-generation oral gavage reproduction toxicity study in rats with a test material identified by the CAS# 122384-87-6 and composed of 43% alkyl phenate sulfide oligomer, 50% highly-refined lubricant base oil and 6.7 wt % free unreacted TPP. The NOAELs and affected endpoints for unreacted levels of TPP present in the alkyl phenate sulfide test material show a strong correspondence with those of a 2-generation dietary toxicity study on commercial grade TPP (Edwards et al. 2012a). This correlation again supports the weight-of-evidence that implicates TPP as the causative agent for the adverse systemic and reproductive effects seen with commercial alkyl phenate sulfides.

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|  | 2-gen alkyl phenate sulfideCAS 122384-87-6 |  | 2-gen tetrapropenyl phenolCAS 210555-94-5 |
| Equivalent free unreacted TPP |  |  |
| Parental effects NOAEL | 3.4 mg/kg/day |  | F0 = 15 mg/kg/day;F1 = 1.5 mg/kg/day |
| Reproductive effects NOAEL | 20 mg/kg/day |  | F0, F1 = 15 mg/kg/day |
| Neonatal toxicity NOAEL | 3.4 mg/kg/day |  | F1, F2 = 15 mg/kg/day |

An additional study, which is not cited in the Human Health Tier II assessment for Long Chain CA phenol derivatives, is highly relevant to the current proposal to classify this category of substance as a reproductive hazard. This 1-generation oral gavage reproduction toxicity study in rats was conducted on a test material composed of 43% alkyl phenate sulfide oligomer, 50% highly-refined lubricant based oil and 0.1-0.2 wt % free unreacted TPP. This test sample was therefore representative of the typical oligomeric composition of the alkyl phenate sulfides covered by this category approach *but with substantially lower levels of unreacted TPP*. As such, this study is considered to assess the reproductive toxicity potential of alkyl phenate sulfide oligomers independent of any confounding contribution of residual TPP. In this study, the NOAEL values for parental, neonatal, and reproductive toxicity were identified as 1000 mg/kg/day. The test substance did not cause effects to fertility, estrous cyclicity, ovary weight, or reproductive organ histopathology (*Edwards TL., et al. 2012b)*. A Robust Study Summary is attached for further consideration (XC9483-FullRSS).

The weight-of-evidence of all the data presented herein demonstrates that the alkyl phenate sulfide oligomers themselves do not account for the reproductive toxicity seen in other studies where a higher level of residual TPP was evident. Together with the strong similarity of the adverse reproductive effects observed with neat TPP (CAS# 210555-94-5), the preponderance of available experimental data clearly demonstrate that the reproductive classification should be assigned to the residual TPP present in this chemical category rather than being assigned to the oligomeric alkyl phenol sulfides themselves.

Additionally, a proposal for a TPP threshold for the classification of mixtures (including Long Chain CA Phenol derivatives placed on the market) below which these effects would not be expected to be observed in rats has been developed by one ATC Member Company based on reproductivity toxicity data for neat TPP and different Long Chain Ca Phenol derivatives containing known amounts of unreacted residual TPP.

Mechanistic studies

Female pubertal assays with commercial grade TPP show statistically significant effects on uterine weight, ovary weight, and time to vaginal patency over a dose range of 60 mg/kg/day and higher (NOAEL = 20mg/kg/day) (Knapp 2007). However, a female pubertal assay performed on a C10 – C15 alkyl phenate sulfide oligomer which was depleted of TPP to a level of < 0.1 wt% produced no statistically significant effects on ovary or uterine weights or changes in time to onset of vaginal patency up to a maximum dose of 1000 mg/kg day alkyl phenate sulfide oligomer (Knapp 2008). These studies demonstrate that whereas commercial grade TPP produced effects in the female pubertal assay at fairly low doses, high doses of alkyl phenate sulfide *depleted of TPP* did not produce significant findings in the same assay. Taken together these data provide substantial support to the conclusion that alkyl phenate sulfide oligomers are not the causative adverse agent in reproduction studies with this category of chemicals.

Conclusion

Weight-of-evidence from toxicokinetic considerations, repeated-dose studies and a mechanistic assay indicates that the reproduction toxicity observed with commercial alkyl phenate sulfides are not due to the oligomers themselves but rather to unreacted TPP. The IMAP document states that unreacted TPP is an integral part of commercial alkyl phenate sulfides, which serves as the basis for assigning the reproduction classification to the alkyl phenate sulfides. However, free unreacted TPP is a non-integral residual by-product of the alkyl phenate sulfide manufacturing process. Manufacturing process optimization can significantly reduce the concentration of unreacted TPP to levels that have been shown not to cause adverse effects in experimental reproduction toxicity studies.

Therefore, ATC respectfully request that the Australian authorities reconsider the recommendation to assign a reproduction category classification to the alkyl phenate sulfides identified by the CAS numbers listed. Rather, commercial products should be classified according to preparation/mixture algorithms based on the free unreacted content of TPP, the known and classified reproductive toxicant constituent. In this way, there will be no commercial disadvantage to companies who have already acted to reduce TPP content to the lowest level possible to improve the safety of their additives and to reduce the need for classification of downstream products. Further there is little justification that such downstream products should be assessed and classified for reprotoxicity based on the total alkyl phenate sulfide content, which would be the consequence of the current NICNAS recommendation. This is because information on such mandatory substance classifications would pass through the supply-chain mainly via disclosure in the Safety Data Sheets, and would have to be utilized by downstream users in their own classification and labelling activities.

References

Edwards T.L. (2012a). A dietary two-generation reproductive toxicity study of tetrapropenyl phenol in rats. WIL Research Laboratories, LLC Study No. WIL-186053.

Edwards TL., et al. (2012b). An oral (gavage) One-Generation Reproductive Toxicity Study of XC9483 (TS09012) in Rats. WIL Research Laboratories, LLC, Study No. WIL-187118.

Annex VI, Section 2.1 (p558) in Guidance on the application of the CLP criteria. Guidance to Regulation (EC) No 1272/2008 on classification, labeling and packaging (CLP) of substances and mixtures. Version 3.0. November 2012

Knapp J.F. (2005). An oral (gavage) one-generation reproductive toxicity study of tetrapropenyl phenol in rats. WIL Research Laboratories, LLC Study No. WIL-186033.

Knapp J.F. (2007). A female pubertal assay of TS03018 administered orally in juvenile female rats. WIL Research Laboratories, LLC Study No. WIL-187058.

Knapp J.F. (2008). A female pubertal assay of TS05005 administered orally in juvenile female rats. WIL Research Laboratories, LLC Study No. WIL-187074.