HEAL Comments regarding proposal for identification of the group of PDDP substances as SVHCs under REACH article 57(c) and article 57(f)

22nd April 2021

The Health and Environment Alliance (HEAL) thanks the German Competent Authority for its proposal to identify the group of substances Phenol, alkylation products (mainly in para position) with C12-rich branched or linear alkyl chains from oligomerisation, covering any individual isomers and/ or combinations thereof (PDDP) as substances of very high concern, under REACH article 57(c) as meeting the criteria for classification in the hazard class reproductive toxicity category 1B, and under article 57(f) due to their endocrine disrupting properties relevant for human health and the environment. We fully support this proposal.

The supporting dossier is well structured and justified.

Key points

- Hazard classification proposals that provide information for classification of groups of substances should be quickly implemented without delays particularly when they concern human health hazards. The classification of some PDDP substances as reprotoxicants category 1B is based on a RAC opinion from 2013, which concluded that such classification should apply to any substance that contain C12 (branched) alkyl-substituted phenols. Therefore, the SVHC listing is warranted for the proposed PDDP group.
- Available rodent studies clearly show that exposure to PDDP is associated with serious adverse and irreversible effects in relation to fertility and the reproductive function in humans.
- The cross-species extrapolation of adverse effects, when there is strong evidence on the similar mode of action (e.g. in vitro ER binding and activity in different species) and there are concerns on adverse effects to other species (due to AOPs in fish), is welcome. It makes the case for the environment disruption potential for both human health and the environment for the proposed group of substances.
- We support that adverse effects on fertility and reproduction should always be considered to have a population relevance without further investigation. Because of the seriousness and irreversibility of such effects, the PDDP group can be considered as endocrine disruptors relevant that meet the criteria of equivalent level of concern (ELoC).

Toxicity for reproduction

PDDP is a group of substances of phenol alkylation products, among them Phenol, dodecyl-, branched (PDB) (CAS 121158-58-5), which was classified in the hazard class reproductive toxicity category 1B (H360F) in 2013. In the Risk Assessment Committee (RAC) related opinion on the classification proposal, it was already stated that "*the harmonised classification will apply to any substance which predominantly contains C12 (branched) alkyl-substituted phenols*". HEAL fully supports this statement and is of the opinion that it makes the case for SVHC identification under REACH article 57(c) of the entire group of PDDP substances.

Endocrine disruptive properties for human health

The available reproductive toxicity studies in rodent clearly show adverse effects on fertility and the reproductive function, particularly in females. A full range of studies is also available to investigate the

endocrine disruptive properties of PDDP substances and they clearly indicate that the observed adverse effects on reproduction are due to the estrogenic action of PDDP. In vitro data indicate interaction with ER, AR, and components of the thyroid hormone system. Both estrogenic and antiandrogenic activity, was found. In vivo studies indicated clear estrogenic effects of PDDP, such as an increase in uterus weight and accelerated vaginal opening in females. Some consistent adverse effects across Level 4 and 5 studies were the reduced ovary weight, decreased corpora lutea and prolongation of the estrus cycle as well as a reduced number of implantations and litter size. In many cases, these effects were observed at the lowest exposure concentration.

The mode of action analysis showed that there was a clear link between molecular initiating event (MIE) of strong ER binding and activation, and the Adverse Outcome (AO) of decreased fertility, with strong evidence for at least four identified intermediate key events (KE).

Endocrine disruptive properties for environment

Endpoints considered relevant for humans are also considered relevant for the environment, and therefore, the estrogenic properties of PDDP apply to all mammals. Although no data were generated in vivo in fish, the limited in vitro data in fish along with adverse outcome pathways and evidence in scientific literature suggests that PDDP may act as an estrogenic endocrine disruptor in fish as well. We welcome this cross-species extrapolation. Furthermore, since PDDP substances impact fertility and the reproductive functions, the adverse effects are considered population relevant.

These effects on human and environmental health on fertility and the reproductive function are severe and irreversible and therefore the PDDP substances equal level of concern as those of CMR Cat 1, PBT or vPvB substances.

For all the reasons stated above, HEAL supports the identification of PDDP substances as SVHC under REACH article 57(c) and article 57(f) respectively.