Comments submitted by the members of the DAPD Consortium on behalf of the Registrants of the Substance below, related to the request for comments to the harmonised classification and labelling proposal by Germany[1]

Substance:
Name: 1,4-Benzenediamine, N,N'-mixed Ph and tolyl derivs.
CAS Number: 68953-84-4
EC Number: 273-227-8

This document includes non-confidential information.

Purpose: Comments to the CLH proposal

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[1] https://echa.europa.eu/documents/10162/84d7f9d8-9bbf-9870-a0ab-b21d5e8d37b8

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1. Introduction

These Comments are submitted jointly by the members of the DAPD consortium, the registrants of the substance 1,4-Benzenediamine, N,N'-mixed Ph and tolyl derivs. CAS Number: 68953-84-4, EC Number: 273-227-8, as comments to the public consultation on a harmonised classification and labelling (CLH) proposal by Germany.

The present Comments address the scientific and legal soundness of the proposed CLH proposal as Skin Sensitiser category 1 ("Skin Sens. Cat. 1") and toxic for reproduction category 1B ("Repr. Cat. 1B") for fertility and development.

Further to this Introduction and the following Background and Summary, and Overall Conclusion sections, this document contains five main sections:

- Comments specific to the skin sensitisation classification proposal, which in general do not disagree with the position that sub-categorisation of classification is not possible based on the available data.
- Comments regarding reproductive toxicity for fertility, which contend that the absence of maternal toxicity is not conclusive and the presumption of human relevance of the observed effects is unjustified.
- Comments regarding reproductivity toxicity for development, which challenge both the conclusion that a developmental effect occurs and the presumption of relevance to humans.
- Comments concerning the appropriateness of the use of data on other substances for justification of the proposed classification.
- While acknowledging that the proposal is concerned with hazard classification, information is included regarding potential exposure and risk from the substance, that should also be considered to contextualise the need and potential benefits for the proposed classification.

2. Background and Summary

The chemical product, diaryl-p-phenylene diamine (DAPD or BENPAT, CAS 68953-84-4 and EC 273-227-8), is used as an anti-degradant in the polymer matrix of tires and industrial rubber products and was registered according to the EU REACH regulation for the 1000+ MT/year tonnage band.

In 2013, DAPD was added to the Community Rolling Action Plan (CoRAP) list, and then subject to the Substance Evaluation procedure (SEv).a Final Decision Letter (FDL) was issued in 2015. The outcome of the evaluation resulted in, amongst others, the request for further information and interpretation on the Reproductive Toxicity endpoint. As a response to the FDL, Full Study Reports with annexes were provided to the eMSCA (Germany) for the reproductive toxicity studies included in the registration dossier.

This section provides a summary of the toxicity data from laboratory studies pertaining to potential reproductive effects of DAPD [Polystay 100 (1,4-Benzenediamine, N,N'-mixed Ph and tolyl derivs., also called BENPAT or DAPD)], and to propose an appropriate classification based upon available data. Classifications of chemicals can be achieved according to their physical, ecological and human health properties through a variety of means, primarily through the development of a range of

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laboratory data. In the case of DAPD, information that is available and applicable for this purpose includes the following:

- A study was conducted to assess potential effects on in utero anatomical development in rats following DAPD exposures to their mothers during gestation days 6-15. This period coincides with the embryonic growth phase in rats. No birth defects were observed in pups, demonstrating a lack of adverse developmental effects on offspring.
- Toxicity testing has evaluated the impacts of DAPD exposures on the reproductive health and function of male and female adult rats. This study determined there was no reproductive toxicity induced in males nor was there evidence of malformations in the pups born to DAPD-exposed females, however a number of effects were observed. Most delivery and offspring findings were observed in the presence of maternal effects but some effects were observed in the low dose weanling animals in the absence of apparent maternal toxicity.
- A satellite study confirmed the DAPD-induction of maternal and offspring effects, and further demonstrated DAPD exposure during the maternal gestational period was needed to induce the reproductive effects.
- There are data and evidence from the screening of other substances which have been assigned classifications considered applicable for DAPD. These include non-steroidal anti-inflammatory drugs (NSAIDs) such as acetylsalicylic acid and a substance chemically related to DAPD - diphenyl-p- phenylenediamine (DPPD).
- For both of these examples, available data supports a proposal of a prostaglandin inhibition mechanism leading to the reproductive effects (e.g. delayed parturition and difficult deliveries). Prostaglandins are known mediators of uterine activity during parturition, and substances that inhibit this action may cause interruption and delays in delivery of offspring. Prostaglandins (PGs) regulate numerous maternal–fetal interactions during pregnancy including preparing the cervix for parturition as well as maintaining normal blood circulation in the fetus.
- However, the available data on other substances do not support that a PG inhibition effect in humans can be considered Repr. Cat. 1B for either development or fertility.

In order to classify chemicals as a reproductive toxin Category 1, data from animal studies should provide clear evidence of specific reproductive toxicity in the absence of contributing systemic toxic effects, i.e. reproductive effects should not be secondary to maternal effects. In the case of DAPD, other toxic effects were observed in dams with potential influences on reproductive endpoints.

Also, in common with the NSAIDs, there is no evidence of reproductive toxicity of DAPD in humans. DAPD's reproductive/maternal effects in rats portrays the many similarities in the reproductive toxicities of salicylic acid, acetylsalicylic acid, and the DAPD-related chemical DPPD. These latter three chemicals qualify for ECHA classification as "suspected human reproductive toxicant" Repr. Cat. 2; H361.

The combination of DAPD study results indicates that the animal evidence for DAPD is insufficient to consider this chemical a presumed human reproductive toxicant, and that the category 2 classifications of other chemicals (related by chemical class or reproductive toxicity profiles) support that DAPD meets the criteria for a Reproduction Category 2 classification.

Considering the lack of a solid basis pointing to a strong presumption of reproductive toxicity effects as required by the CLP Regulation, the registrants of DAPD consider that that the CLH proposal of Repr. Cat. 1B by the eMSCA (Germany) is not appropriate and is insufficiently justified.

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3. Skin Sensitisation assessment

a) The DAPD Consortium members have minor comments on the proposed harmonised classification of Skin Sensitizer category 1 without further sub-categorisation.

b) It is recognised that the available study data were performed at an induction dose that does not allow to compare to the sub-categorisation criteria. However, despite that, a self-classification of Skin Sensitiser 1B was already precautionarily assigned by the registrants. It is also recognised that a consitituent of DAPD, that is DPPD, already has a harmonised classification of Skin Sensitiser 1.

c) To the current knowledge of the consortium members, human data such as patch testing is not routinely performed on DAPD at manufacturing or downstream user sites. As a standard approach, such testing is only performed where a sentisation issue is identified, such to identify the source. The absence of such data would hence tend to suggest that no sensitisation issues exist with DAPD, even though it is acknowledged that this does not allow to prove that it does not.

d) Therefore, even though it could be concluded that sub-categorisation of skin sensitization is not possible, the Consortium members do not exclude that a testing proposal could be submitted to perform further testing to clarify the sub-categorisation, if desired and approved.

4. Comments specific to Reproductive Toxicity for fertility

a) The DAPD Consortium members acknowledge that the available studies on the reproductive effects of DAPD demonstrate the presence of dystocia in Spague-Dawley rats, leading to maternal and pup mortality. It is also acknowledged that dystocia is established as an adverse effect on fertility.

b) However, contrary to the position established in the classification proposal, the Consortium contends that there are sufficient doubts that i) the dystocia was not secondary to maternal toxicity and ii) there is sufficient basis to presume the same effect being likely to occur in humans. Furthermore the classification proposal does not appear to consider a large body of evidence on Salicylic acid (Aspirin) which should be a clear comparison point for establishing the extent of relevance to humans, and thus clarifying between the Repr. Cat. 1B or Repr. Cat. 2 classification.

4.1. The absence of maternal toxicity effect is not established

a) One aspect for determination of the difference between the Repr. Cat. 1B and Repr. Cat. 2 classifications is to establish whether any reprotoxic effects are present in the absence of maternal toxicity.

b) The toxicity profile of DAPD to rats has been established through three repeated dose toxicity studies, of which the key 52-week chronic dietary study (Iatropoulos, 1996) established a NOAEL of 16 mg/kg bw/day. The observed effects in this study included elevated organ weights (e.g. for liver, kidney and spleen) in the mid and high dose animals.

c) The histopathologic examination at week 52 showed that the spleen and liver exhibited signs of extramedullary erythropoiesis in the high dose male and female groups. Hematologic changes included elevated mean corpuscular volumes and decreased mean corpuscular hemoglobin in high dose males and females.

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d) These findings suggest a macrocytic anemia in the high dose animals. In the subsequent key two-generation reproductive toxicity (OECD 416) study (Tyl, 2000a), statistically significant maternal and reproduction effects were observed in dams and pups, including prolongation of gestation length (inhibition to parturition), decreased litter sizes (total or live pups/litter), and increased pup weights. As one further consequence to these effects, maternal mortality was observed, mostly at the higher dose (approx. 113 mg/kg bw/day), which can be attributed to the elevated occurrence of dystocia.

e) However, other observations were made that reflected maternal toxicity due to DAPD. Clinical observations of mid- and /or high-dose F0 and F1 dams indicated elevated incidences of pale eyes, piloerection, and unscheduled deaths. Dams with unscheduled deaths in the mid- and high-dose groups displayed gross abnormalities of the kidney (pitting, paleness, discoloration), liver (thickening, firmness, pale foci), and uteri (retained placenta & foetuses, resorbing implants).

f) Although it is acknowledged that the maternal toxicity in the two-generation study could have been, at least partially, a result of effects to the parturition process and the difficulties giving birth, in light of the known toxicity of DAPD to rats at considerably lower concentrations (NOAEL of 16 mg/kg bw/d vs two generation reproductive toxicity study effects mostly observed at 113 mg/kg bw/d), as determined by repeated dose testing, it also cannot be excluded that the observed toxicity, to some degree, caused the dystocia. In that respect, the absence of maternal toxicity definitely cannot be concluded as a basis for assessing the effects against the criteria.

4.2. Conclusion of presumed relevance to humans is unjustified

a) 10. The three available studies performed for DAPD reproductive toxicity assessment were all conducted using Sprague-Dawley (SD) rats. Apart from the fertility effects, there were also histological changes to the kidneys in all generations. In the prior repeated does toxicity studies, Fischer 344 rats were used. In these studies, despite exposure for up to 52 weeks, there was no occurrence of the same effects to the kidneys. This indicates, at least for one specific effect, that effect differences exist between different strains of rats.

b) In the absence of reproductive toxicity studies in other rats strains or species, the registrants of DAPD thus consider that there is sufficient reason to doubt that the same reproductive effects would be observed. Therefore the presumption by the proposal that the reproductive effective observed in SD rats would be relevant to humans is flawed and lacking justification. Taking all the available information into account, including that of the repeated dose toxicity, it cannot be presumed that the reproductive effects would also exist in other species, e.g. rabbit, humans, etc.

c) 11. In reference to the above comments on the relevance of the effects on other species, it is highlighted that the DAPD dossier does not contain a Post Natal Development Toxicity study (OECD 414) in a second species (not rat), as, in March 2020, the Consortium submitted a data waiver. To date, this data requirement was considered unnecessary due to the ongoing assessment of reproductive toxicity by Germany, based on their agreement that further reproductive toxicity studies are not required. It is thus noted that, in the absence of such study, the legitimacy of presumption of toxic effects of DAPD being relevant across different species is weak. The registrants of DAPD would however be open to further discussion on the means to clarify this point.

d) The classification proposal makes significant references to reproductive toxicity studies conducted on the substance DPPD, which is a constitutent (± 20%) of DAPD. One of those (Marois, 1998) develops a mode of action proposal of prostaglandin inhibition based on the effects being

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preventable through injection of prostaglandin F2α. These data support the concept that prostaglandins may have a central role in the process of parturition, and that prostaglandin inhibition likely is an important factor in the delay of this process in DPPD and DAPD-treated rats.

e) However, the development of a link between prostaglandin inhibition and dystocia in rats does not serve to provide any proof or basis for presumption that the same link (or degree of severity there-of) would exist in other larger species, and especially humans.

f) This is furthermore highlighted in more recent research as reviewed and compiled by Sugitomo (2015) and Mitchell (2009). The authors describe that parturition in rats starts by the release of prostaglandin (specifically $PGF_{2\alpha}$), which causes luteolysis. Throughout gestation, the corpora lutea is the main source of progesterone. This hormone is essential to sustain the pregnancy. Following luteolysis, the progesterone levels drop, and – as the pregnancy is no longer sustained – the parturition is initialized.

g) However, the same authors also state that parturition in humans is a more complex and less understood process. In humans, the placenta takes over the progesterone production from the corpora lutea in the course of the pregnancy. Hence, prostaglandin-induced luteolysis is not the trigger for parturition in humans.

h) Additionally, human parturition is not typically accompanied by a drop in the progesterone levels. Where the path leading to parturition seems to be a linear step-by-step process in rats, the authors suggest that human parturition occurs via modular accumulation of physiological systems, where “multiple independent and interdependent modular physiological systems develop in parallel, eventually achieving a critical mass that culminates in parturition”.

i) In this respect, Mitchell states explicitly that the “entire physiological basis for uterine activiation and parturition in the vast majority of currently used models is overly simplified”, in particular when it concerns animal models that occur through initiation of parturition via luteolysis, like is the case in the rat.

j) It is furthermore noted that apart from induction of luteolysis, prostaglandines also have (*inter alia*) an uterotonic acitivity, inducing contractions of the uterus. This uterotonic activity is expected to be of relevance both in rats and in humans.

k) Given the significantly more advanced biological processes in humans compared to rats, it is quite plausible that prostaglandin has a much less significant role in the parturition process in humans. Thus the proposal’s presumption of relevance of the effect to humans is unjustified.

4.3. Proposal does not consider known analogous effects with Salicylic acid

a) The DAPD dossier contains an extensive document which summarises the available data relevant to DAPD and reproductive toxicity, and justifies the basis for the self-classification of DAPD as Repr. Cat. 2 ‘suspected human reproductive toxicant’. Contained in that document is an assessment of the similarity of effects observed with a common human use substances salicylic acid (SA) and acetyl salicylic acid (ASA).

b) These non-steroidal anti-inflammatory drugs in turn provide important insight into the potential relevance of effects in humans. Furthermore, a full RAC assessment is already available for SA (2016). The submitted proposal makes no mention of this self-classification document, nor of comparison of DAPD effects to those of SA and ASA.

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c) To that extent, it appears that the proposal submitter has disregarded information available in the dossier, and not taken all available information and data into consideration. For completeness, a summary of the information on SA and ASA contained in that document is provided in these submitted comments.

d) Results in reproductive/development toxicity studies in rats with ASA (acetyl salicylic acid) demonstrate embryo/fetotoxic effects such as dose-dependent growth delays, foetal death and malformations. SA dosed at high dose of 0.4% dietary level (205.9 mg/kg bw) in pregnant rats induced maternal effects expressed as temporary body weight loss with toxic symptoms (salivation, piloerection) and foetal effects [high fetal mortality, high frequency of complex anomalies (cranioschisis, myeloschisis, oligodactyly, etc.)] and dose-related foetal growth retardation. Litter size and body weight/length as well as tail length were statistically significantly decreased. At a dose of 0.2%, the body weight/length and the tail length were statistically significantly decreased (ECHA RAC Salicylic acid, 2016).

e) A post-embryonic maternal exposure study was designed in Sprague-Dawley rats to study the dose-response relationship for salicylate-related effects on labour and gestation, and the relative potency of SA as compared with ASA for these reproductive effects. Pregnant females received oral doses of 20, 80, or 200 mg/kg/day sodium salicylate, or 260 mg/kg/day ASA as a positive control, on days 15 through 21 of gestation. Onset of labour was followed in each animal beginning on day 21 of gestation.

f) The data failed to demonstrate a substantial potency difference between ASA and SA but some differences in toxicity were observed. Relative to controls, gestation times were unaffected by SA. SA treatment resulted in a dose-related trend towards increased duration of labour which was statistically significant at 200 mg/kg/day of SA. ASA treatment of pregnant females resulted in both prolonged labor and gestation times.

g) Both the highest administered dose of SA and ASA treatment contributed to increased maternal peripartum death. Overall, the study confirms a dose-response relationship for SA-induced maternal reproductive effects and supports a NOEL for this compound of 80 mg/kg/day for adverse effects on parturition (Davis et al., 1995).

h) The reproductive toxicity evaluation of SA concluded that a NOAEL of sodium salicylate administered orally to mated rats has been established to 80 mg/kg bw/d corresponding to 69 mg/kg bw/d of salicylic acid. The results also showed that following oral administration salicylic acid is neither teratogenic nor embryotoxic up to 75 mg/kg bw/d in rodents and up to 100 mg/kg bw/d in monkey. Above these dose levels, foetal malformations (skeletal malformations, cleft lip, and growth retardation), resorptions and perinatal death were recorded with salicylic acid or acetylsalicylic acid.

i) A study in monkeys (Wilson, 1977) also showed teratogenic properties with ASA at high doses but with lower magnitude. ASA given to pregnant monkeys at doses of 100 and 150 mg/kg bw (twice daily, for 10 days starting on gd 23) resulted in growth retardation, abortions or resorbed foetuses. The high dose also induced malformations such as gross abnormality, cranioschisis and cystic kidney. In rabbits (Cappon, 2003), effects were not teratogenic, but limited to slight growth retardation and only at doses much higher than those active in rats and monkeys.

j) In humans, ASA doses up to 100 mg/d are generally considered safe during pregnancy. For doses exceeding 500 mg/d, the concern is related to effects caused by prostaglandin synthesis inhibition having a negative impact on pregnancy and/or foetal development. During the third

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trimester, all prostaglandin synthesis inhibitors can lead to the following in the foetus: heart/lung toxicity (with a premature closure of the Ductus arteriosus and pulmonary hypertension), and renal dysfunction including renal failure. In the mother and the new-born baby at parturition, the high doses can lead to possible anti-coagulant prolongation of the bleeding time, and inhibition of uterine contractions leading to delayed or prolonged delivery.

k) Studies have failed to derive a conclusion on the potential of ASA to induce malformations in humans. Low doses used in therapy and the absence of reliable epidemiological evidence are often invoked as explanations. When used during pregnancy, a precautionary dose range and duration of medication are recommended. Thus, ECHA's RAC recommends no ASA dosing above 100 mg/d during the third trimester (ECHA RAC Salicylic acid, 2016).

l) ASA is known to induce pain relief in part due to its prostaglandin inhibitory activity. Prostaglandins are also known mediators of uterine activity during parturition, and substances that inhibit this action may cause interruption and delays in delivery of offspring as seen for ASA. Prostaglandins (PGs) regulate numerous maternal–fetal interactions during pregnancy including preparing the cervix for parturition as well as maintaining normal blood circulation in the fetus. Drugs like ASA block PG synthesis, and thereby reduce uterine contractions plus serving to prevent preterm delivery (Reese et al., 2000).

m) While neither ASA nor SA is a definitive reproductive or developmental toxin in humans, the evidence in rats and monkeys justified its classification by the Risk Assessment committee (RAC) as a developmental toxin (Repr. Cat. 2; H361d "Suspected of damaging the unborn child" (ECHA RAC Salicylic acid, 2016)). The committee also concluded that there is insufficient evidence that salicylic acid exhibits adverse effects on sexual function and fertility, and thus no classification for salicylic acid fertility is justified.

n) The available information on SA and ASA, especially in respect to comparison of doses and effects in rats vs other species, gives sufficient justification that chemicals producing prostaglandin inhibition cannot be presumed to cause equal effects across all species. This further supports the the classification proposals' presumption of human relevance for the observed reproductive effects is not justified, and incorrect.

5. Comments specific to Reproductive Toxicity for development

a) The DAPD Consortium members acknowledge that the available studies on the reproductive effects of DAPD demonstrate the presence of polycystic kidneys in Spague-Dawley rats.

b) However, contrary to the position established in the classification proposal, the Consortium contends that there are sufficient doubts that i) the kidney effect is a developmental effect, but rather a direct toxicity effect and ii) there is sufficient basis to presume the same effect being likely to occur in humans.

5.1. Polycystic kidneys is toxicity effect, not developmental

a) In regards to reproductive developmental effects, the submitted proposal highlights the incidents of polycystic kidneys, particularly in F1 and F2 offsping. The proposal excludes the possibility of these effects being due to toxicity, due to the low incidents in F0 females and absence of such effects in the oral toxicity studies conducted.

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b) Furthermore, the data on the available prenatal development toxicity study (RTI, 1995), which shows an absence of malformation in embryonic kidneys, is discarded by the Proposal on a presumption that dosing was performed during gestational days that *might not* be not relevant for the forming of kidneys. This presumption is however not validated with other data or studies.

c) The registrants of DAPD consider that the kidney findings of uncertain toxic impact were noted in both adults and weanlings. Termed "polycystic kidney", the lesion was visible grossly, and microscopic exams were only made if gross identification of cysts were made. The finding was observed in a dose-related manner in all generations of rats with increasing incidences and severities ranging from minimal to marked. These polycystic changes were sporadically observed in parental F0 rats (NOEL 400 ppm, approx. 60 mg/kg bw/d) and more frequently in weanlings in both the F1 and F2 generations (NOEL <120 ppm, < 20 mg/kg bw/d). These lesions persisted from the weanling stage in F1 animals into adulthood but since these F1 rats were continuously exposed into adulthood, the potential reversibility of the renal lesions could not be ascertained.

d) Histological changes were observed in the kidneys at the various generations, including F0 adults, F1 weanling, F1 adults and F2 weanlings. The polycystic changes were associated with other findings such as cortical necrosis (F0 adults), renal tubule dilatation, chronic inflammation and nephropathy (F1 adults), and renal tubule regeneration (F1 weanlings & F1 adults, F2 weanlings). Findings might be due to direct toxic effects, but also to the low water solubility of the substance. The renal tubular regeneration, however, indicates that the kidney findings are most likely of reversible nature.

e) Thus the registrants of DAPD contend that effects to the kidneys were indeed observed at the highest dose of F0 females (33%) occurrence. This alone indicates that some toxicity effect does exist towards the kidneys.

f) Further, the registrants of DAPD contend that in adult kidneys the ability to filter and negate the toxic effect of DAPD is much more developed that in weanlings where the kidneys are still developing. This is validated by the data showing that the occurrence of polycystic kidneys in F1 weanlings (40%-95% in higher two doses) drops to 18%-65% in F1 adults. This indicates that as the kidneys develop they increase ability to clear the toxic effects, and thus the effects are not a permanent developmental effect.

g) In these regards, it is worth mentioning that, as it is apparent from the *travaux préparatoires* of Regulation (EC) No. 1906/2006,[2] substances that are carcinogenic, mutagenic and reproductive toxicants are subject to a specific regulatory regime due to the irreversibility of effects. As the General Court specifies, the "[t]*he EU legislature therefore considered that, by their nature, the effects of those substances on human health give rise to concerns of such a level that differentiating them from all other substances, including those falling within other hazard classes that may result in death or other irreversible effects, is justified*".[3]

h) Thus, the registrants of DAPD contend that the observed polycystic kidneys are a direct result of exposure to DAPD, with evidence of reversibility from kidney development, and thus is a toxicity-

[2] Proposal for a Regulation of the European Parliament and of the Council concerning the Registration, Evaluation, Authorisation and Restriction of Chemicals(REACH), establishing a European Chemicals Agency and amending Directive1999/45/EC, available at https://www.europarl.europa.eu/RegData/docs_autres_institutions/commission_europeenne/com/2003/0644/COM_COM(2003)0644_EN.pdf

[3] C-323/15 P, *Polynt v ECHA*, ECLI:EU:C:2017:207, paragraph 38.

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related effect and not a developmental effect.

5.2. Kidney effect is not observed in other species, undermines assumption for human relevance

a) As already elaborated in paragraphs 6 and 10 above, repeated dose toxicity studies that were conducted on DAPD using Fischer 344 rats showed no adverse effects on the kidneys. This indicates that the effects observed from exposure to DAPD are at least rat strain dependent, and thus very possibly also species dependent.

b) The Proposal ignores this clear difference in effects between strains, and leaps to presumed human relevance. In the absence of further reproductive toxicity studies in other species, the registrants of DAPD thus consider that there is sufficient reason to doubt that the same kidney effects would be observed. Therefore the presumption by the proposal that the effective observed in SD rats would be relevant to humans is flawed and lacking justification.

c) Taking all the available information into account, including that of the repeated dose toxicity, it cannot be presumed that the effects, regardless of whether toxicity or developmental, would also exist in other species, e.g. rabbit, humans, etc.

6. Comments to the use of studies on DPPD and DPA for the assessment

a) At several points of the classification proposal assessment, significant references are made to studies and data available on both DPPD (cas no. 74-31-7), a constituent (±20%) of DAPD, and DPA (cas no. 122-39-4), a known impurity of DAPD. These references are used as basis for justification of the Repr. Cat. 1B classification proposal.

b) The registrants of DAPD contend that, although the references are valid and relevant to DAPD, they cannot robustly support a Repr. Cat. 1B classification until such time that either substance is assessed to also have presumed reprotoxic affects in humans.

c) The failure to align the regulatory process and classifications on these substances, together with DAPD, would have unintended consequences, potentially negating the objective of the classification of DAPD.

6.1. *DPPD is classified Repr. Cat. 2, thus should not be used as justification for Repr. Cat. 1B*

a) As mentioned in paragraph 12 above, the submitted proposal makes reference to several studies on DPPD for reinforcing both the observed reproductive effects and to propose a potential mode of action. The proposal uses this further information on DPPD as part of the justification for the proposed Repr. Cat. 1B classification.

b) However, it is important to note that DPPD already has a harmonised classification and labelling according to Annex VI to the CLP Regulation and does not have any classification for reproductive toxicity endpoint. **DPPD** does however carry a self-classification of **Repr. Cat. 2** and not as Repr. Cat. 1B.

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c) In this context, the registrants of DAPD contend that, at this stage, the data on DPPD can only further support the existing **Repr. 2 classification for DAPD**, and provides no basis for a Repr. Cat. 1B classification.

d) The registrants thus submit that if the studies on DPPD are to be used as representation and justification for the reproductive toxicity effects of DAPD, then only two options are (legally and scientifically) valid:

   i) Either, a harmonised classification and labelling proposal and decision on the reproductive toxicity endpoint is first concluded on DPPD, before any action is taken on DAPD;
   ii) Or, the data available on DPPD is consistently read across to DAPD for the purposes of a harmonised **Repr. Cat. 2 classification**.

e) Although DPPD does not have a harmonised classification as Repr. Cat. 2, it would appear contradictory to use the data available on a constituent of the substance and supporting a Repr. Cat. 2 classification for the purposes of achieving a Repr. Cat. 1B classification for the substance containing such constituent, without any credible explanation as to why such data supported a different classification. This is all the more true since the constituents are an integral part of a substance.

f) Should DAPD be classified as Repr. Cat. 1B based on the data available on DPPD, the legal act establishing the harmonised classification may be vitiated by a manifest error of assessment.[4]

6.2. *DPA harmonized classification does not include reprotoxicity*

a) Similarly to section 6.1 above, Diphenylamine (DPA), an impurity of DAPD (< 2%) is heavily referenced in the Proposal in regards to the incidence of polycystic kidneys.

b) It is noted that DPA already has a harmonised classification and labelling according to Annex VI to the CLP Regulation, which does not include any classification for reproductive toxicity endpoint. Furthermore, DPA does not have any self-classification for reproductive toxicity.

c) In this context, the registrants of DAPD contend that the data on DPA provides no basis for a Repr. Cat. 1B classification for DAPD.

d) The registrants thus propose that if the studies on DPA are to be used as representation and justification for the reproductive toxicity effects of DAPD, then the only (legally and scientifically) valid option is a harmonised classification and labelling proposal and decision on the reproductive toxicity endpoint should first be concluded on DPA, before any action is taken on DAPD.

e) In fact, it would appear contradictory, and scientifically unsound, to use the data available on an impurity not even classified as Repr. Cat. 1B to support this classification for the substance, without any credible explanation as to why such data supported such classification.

f) Should DAPD be classified as Repr. Cat. 1B based on the data available on DPA, the legal act establishing the harmonised classification may be vitiated by a manifest error of assessment. [4]

[4] Case T 689/13, *Bilbaína de Alquitranes and Others v Commission*, paragraphs 28-34.

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7. Comments regarding the use and potential exposure of the substance

a) It is fully acknowledged by the registrants of DAPD that the subject of these comments is one of determination of the hazard classification. As such, comments and contributions in related to use, exposure, and risk are not specifically germane.

b) However, to put into context how the observed reproductive effects, in the unlikely case relevant to humans, are unlikely to actually occur in humans, we submit the below further comments regarding potential use and exposure.

c) As a further introductory comment, the registrants of DAPD wish to note that the uses identified in the ECHA disseminated dossier, and reproduced in the submitted proposal, are of unknown origin and factually incorrect. DAPD is only used principally in tyres, and to some lesser extent in industry rubber products, for example automobile belts, hoses, mounts, or conveyor belts. To that extent, the use is limited to professional users and there are no definitely known consumer uses.

7.1. *Exposure to humans during the life cycle will be low due to existing risk control measures, the absence of bio-availability and proven degradation in water*

a) During manufacturing and downstream use (principally tyre manufacturing), the risks to workers is already completely controlled by the exposure control measures in place as a result of the existing Repr. Cat. 2 classification. These include: local ventilation, personal protective equipment, control of work assignments/rotation, and good hygiene practices. The registrants of DAPD acknowledge that there could be routes of potential exposure to DAPD to the general population through article service life, principally from tyre wear.

b) In the case of wear from tyres manufactured using DAPD, due to the phys-chem properties of DAPD, principally high Log Kow, and the fact that any DAPD present is bound into a vulcanized rubber matrix, the likelihood of DAPD exposure originating from tyre wear particles is extremely low. Extensive research and publications have been performed on tyre wear particles by the World Business Council for Sustainable Development (WBCSD), which demonstrates that exposure to chemicals from tyre wear particles is very low.[5]

c) Furthermore, any potential leaching of DAPD from a tyre wear particle would initially be driven by contact with water. Due to the very low solubility of DAPD in water (< 0.1 mg/L), transport of DAPD from the tyre wear particle into the water is unlikely to occur. However, in the case that it does, a recent OECD 309 surface water degradation study has demonstrated that DAPD degrades in water with a half-life well below 40 days. DAPD is also phototransformed in both air and water and by UV light, and readily reacts with oxygen.

d) The registrants of DAPD therefore contend that the risk of exposure of the general population to DAPD is extremely low. As such, additional regulatory control measures, such as identification as

[5] https://www.wbcsd.org/Sector-Projects/Tire-Industry-Project/Resources/Tire-and-Road-Wear-Particles-TRWP-and-other-Material-Research.

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a Substance of Very High Concern (SVHC) would not result in a significant risk reduction.

8. Overall conclusions

In summary, the above submitted comments conclude the following points:

- The available studies on the reproductive effects of DAPD demonstrate the presence of dystocia in Spague-Dawley rats, leading to maternal and pup mortality.
- While dystocia is an adverse effect on fertility, contrary to the position established in the classification proposal, the submitted comments contend that there are sufficient doubts that i) the dystocia was not secondary to maternal toxicity and ii) there is sufficient basis to presume the same effect being likely to occur in humans.
- Furthermore the classification proposal does not appear to consider a large body of evidence on Salicylic acid (Aspirin), which should be a clear comparison point for establishing the extent of relevance to humans, and thus clarifying between Repr. Cat. 1B or Repr. Cat. 2 classification. Therefore, the proposal for classification of DAPD as a 'presumed human reproductive toxicant' (Repr. Cat. 1B) for fertility is unjustified.
- In addition, while the available studies on the reproductive effects of DAPD demonstrate the presence of polycystic kidneys in Spague-Dawley rats, contrary to the position established in the classification proposal, the Consortium contends that there are sufficient doubts that i) the kidney effect is a developmental effect, but rather a direct toxicity effect and ii) there is sufficient basis to presume the same effect being likely to occur in humans.
- Therefore, the proposal for classification of DAPD as a 'presumed human reproductive toxicant' (Repr. Cat. 1B) for development is unjustified.
- The classification proposal references studies and data on substances DPPD and DPA, respectively a constituent and an impurity of DAPD, as a basis for justification of the Repr. Cat. 1B proposal. However neither of these substances have been concluded as meeting the criteria of Repr. Cat. 1B. Therefore, in the case that DAPD is classified as Repr. Cat. 1B based on the data available on DPPD and/or DPA, the legal act establishing the harmonised classification may be vitiated by a <u>manifest error of assessment.</u>
- While acknowledging that the CLH procedure is directed towards hazard assessment, in order to contextualise the potential advantages to the control of risks that the proposed classification might achieve, it is submitted that DAPD has been shown to degrade in the environment and thus would not present any risk to man via the environment. Within the manufacturing and down-stream use phases, exposure risks are already controlled as a result of the existing Repr. Cat. 2 self classification. Therefore, no further benefit in risk control can be achieved through to proposed harmonized classification.

➢ **In conclusion, the registrants of DAPD submit that the proposed harmonized classification as Repr. Cat. 1B for fertility and development is inappropriate and unjustified.**

➢ **Furthermore, the basis on which this proposal is reached could be considered to be a manifest error of assessment.**

➢ **Additionally, due to overall absence of exposure to humans at all life cycle stages, the proposal would achieve no further control of risk against the current self-classification.**

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