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German Comments related to the CLH proposal of biphenyl-2-ol

Substance name:	biphenyl-2-ol; 2-phenylphenol; 2-hydroxybiphenyl
CAS Number:	90-43-7
EC Number:	201-993-5
Submitted by	Spain

Current entry in Annex VI of CLP Regulation:

Skin Irrit. 2, H315

Eye Irrit. 2, H319

STOT SE 3, H335

Aquatic Acute 1, H400

Proposed future entry in Annex VI of CLP Regulation:

Skin Corr. 1, H314

Eye Dam. 1, H318

Carc. 2, H351

Aquatic Acute 1, H400

Aquatic Acute 1, M-factor=1

Aquatic Chronic 1, H410

Aquatic Chronic 1, m-factor=1

General Comments:

At several places in the CLH report, the substance is referred to as "including the sodium salt orthophenyl phenol" (e.g. in sections 1.1.3 and 2.1.1). The sodium salt sodium biphenyl-2-olate (CAS: 132-27-4 or 6152-33-6, EC: 205-055-6) is also listed in section 3.6 as "parent substance". In contrast, the sodium salt is neither included in the identity under section 1.3, nor considered for the physical and chemical properties in section 2.2.2. Please consider adding respective information about the sodium salt to the named sections or clarify that it is not addressed by this CLH report.

Note: The passages marked in yellow contain sensitive data that are not published.

Carcinogenicity:

We support the DS's proposal of classifying *ortho*-phenylphenol (OPP; 2-phenylphenol) as Carc. 2 (H351) based on the urinary bladder tumours in male rats.

The key evidence of the urinary bladder findings stems from the chronic toxicity/oncogenicity rat study by [redacted] (1996) ([redacted] two-year, dietary, rat). This study showed a dose- and time-dependent relationship between exposure to OPP and urinary bladder effects leading to increased tumour incidence by 24 months. Prior to bladder tumourigenesis seen in 24 months, hyperplasia and increased calculus formation in the urinary bladder were detected after 12 months of exposure. A number of repeated dose (e.g. two-generation studies) and mechanistic studies appear to confirm the occurrence of hyperplasia and formation of calculus prior to tumourigenesis in the bladder. A non-genotoxic mode of action leading to tumour formation has been postulated.

There were some inconsistencies observed with this finding. A carcinogenicity study by Hodge et al. (1952) (CA B.6.5-01 two-year, dietary, rat) reported no bladder lesion in rats after 2-year exposure to OPP, but the study had many method deficiencies and cannot be considered as reliable for evaluation. A chronic toxicity study by [redacted] (1984) [redacted] 91-week dietary, rat) showed significant number of male rats with bladder tumours at the mid-dose (23 out of 24 rats examined) but not at the high dose (4 out of 23 rats). The scientific reasoning behind the lack of dose-response relationship in this study is unclear, as the study (published in a scientific journal) has limited data reporting that preclude clear evaluation of the outcomes. Nevertheless, this study provides evidence of urinary bladder lesions that is supportive of Carc. 2 classification.

We agree with the DS that the human relevance of the mechanism of OPP leading to urinary bladder in male rats cannot be excluded. As discussed in IARC Scientific Publication No. 147 (1999), while there might be quantitative differences in the carcinogenic response to calculi between species (e.g. urine composition in rats vs. humans), the urinary bladder neoplasms in rats due to calculus formation cannot be considered to be species-specific. Thus, this tumour response in the urinary bladder is relevant for the evaluation of carcinogenicity to humans.

The increased liver tumour incidence in male mice seen in the 2-year oncogenicity study by [redacted] (1995) [redacted] two-year, dietary, mice) appears to be mediated by PPARα activation (as demonstrated in the study by [redacted] (2009) [redacted] gene expression and enzymatic activity study in mouse liver) and is therefore not considered to be relevant for the evaluation of carcinogenicity to humans.

Mutagenicity:

The DS concluded that no conclusion for the classification of genotoxicity/germ cell mutagenicity for *ortho*-phenylphenol (OPP; 2-phenylphenol) could be drawn due to the low reliability of the *in vivo* mutagenicity assay data and insufficient investigation of the clastogenicity potential *in vivo*.

Based on the genotoxicity data (as presented in Tables 50 and 51 of CLH report), OPP is not mutagenic in bacteria and mammalian cells but clastogenic *in vitro*. No *in vitro* data on aneugenicity was available for evaluation. The *in vivo* genotoxicity data of OPP, while mostly negative for OPP, were mainly supporting evidence and considered not robust enough to draw an overall conclusion on genotoxicity with confidence.

Given the clastogenic potential *in vitro*, uncertainty about clastogenicity potential *in vivo* and missing data on aneugenicity, we agree that it is currently not possible to draw a conclusion on genotoxicity/germ cell mutagenicity potential of OPP based on the current data available for evaluation.

According to the EFSA (2017) Scientific Opinion on the clarification of some aspects related to genotoxicity assessment, in cases where it is not possible to conclude on genotoxicity with confidence, the assessor should consider other data such as information on carcinogenicity or reproductive toxicity testing, data from toxicokinetics studies, read-across from structurally related substances and predictions from QSAR models. This additional information (in particular data from read-across substances and QSAR predictions) could be used in a weight-of-evidence approach and could be beneficial for this assessment. We therefore

recommend the DS to take into account any other relevant information for the genotoxicity assessment in order to reduce the major uncertainties and/or to address the gaps in this assessment.

Reproductive toxicity:

The developmental toxicity potential of *ortho*-phenylphenol (OPP; 2-phenylphenol) should be further explored, considering the increased litter resorptions observed in the developmental toxicity rabbit study by [redacted] (1991c; [redacted], rabbit developmental toxicity study), which might be substance-related as re-analysed in a review by Kwok and Silva (2013, CA B.6.6.2-06, developmental toxicity meta-study).

In the [redacted] (1991c; [redacted] Rabbit developmental toxicity) study, an increase of litters with resorption was observed in all treated groups compared to control, and the incidence rates at mid- and highest doses (100 and 250 mg/kg bw/d, respectively) exceeded that of the historical control. However, the study authors concluded that this finding was not substance-related due to a lack of statistical significance or dose-response relationship for this finding.

On the contrary, Kwok and Silva (2013; CA B.6.6.2-06 developmental toxicity meta-study) presented a re-analysis of the data from the [redacted] (1991c; [redacted] Rabbit developmental toxicity) study and showed a dose-related and statistically significant increase of litter resorption when data only from the 1st testing phase of the study was used. We deem this re-analysis valid since in the 2nd testing phase of the study, only 2 control does and 6 does at 250 mg/kg bw/d were investigated (i.e. no low or mid-dose), and it is unclear if there were any differences in the experimental design of the 2 phases.

It is also worth noting that the degree of resorption at the highest dose (250 mg/kg bw/d) might be masked by the high maternal toxicity at this dose (e.g. increased mortality, kidney effects).

If the DS is not convinced by the outcome presented by Kwok and Silva (2013; CA B.6.6.2-06 Developmental toxicity meta-study), then a clearer elaboration is needed as to why the litter resorption at the mid-dose (100 mg/kg bw/d) should not be considered as the LOAEL for developmental toxicity effects in the [redacted] (1991c; [redacted] Rabbit developmental toxicity) study.

Skin corrosion/irritation:

We support the DS's proposal of classifying *ortho*-phenylphenol (OPP; 2-phenylphenol) as Skin Corrosive, Cat. 1 (H314). The GLP-compliant guideline study (OECD TG 404) by [redacted] (1994a; [redacted] Skin

irritation/corrosion study in rabbits with OPP) clearly demonstrates the corrosive potential of OPP as 4 out of 6 tested rabbits experienced persistent erythema starting 30 minutes after exposure with scar formation observed by study day 15. This finding is considered as sufficient evidence for classification for skin corrosion.

Serious eye damage/eye irritation:

We agree with the DS's evaluation on eye damage and subsequent proposal of classifying *ortho*-phenylphenol (OPP; 2-phenylphenol) as Serious Eye Damage, Cat. 1 (H318). Even though there is no study with a 21-d observation period available for the assessment of reversibility of eye lesions, existing data provide indication that the eye effects of OPP might not be reversible. For example, in the [redacted] (1981b; [redacted] acute eye irritation/corrosion study in rabbits with OPP) study, the severity of iritis even increased in 2 out of 3 rabbits and corneal opacity worsened in one rabbit (to grade 3) by study day 8. The supporting studies (e.g. [redacted] (1971; [redacted] acute eye irritation/corrosion study in rabbits with OPP) for OPP and [redacted] (1988; [redacted] acute eye irritation/corrosion study in rabbits with SOPP) for sodium *ortho*-phenylphenate (or SOPP) also demonstrated the persistent nature of the eye lesions (corneal opacity and iritis) in majority of the tested rabbits. Combined with the skin corrosive potential of OPP, the Serious Eye Damage, Cat. 1 classification is justified taking a weight of evidence approach.

Specific target organ toxicity – single exposure:

We are not convinced that the existing harmonised classification of STOT SE 3 (H335) for *ortho*-phenylphenol (OPP; 2-phenylphenol) should be deleted given the corrosive nature of the substance (e.g. classifications of OPP as Skin Corrosive, Cat. 1 (H314) and Serious Eye Damage, Cat. 1 (H318) have been proposed).

In the CLP (2017) Guidance, it is stated that "it is a reasonable assumption that corrosive substances may also cause respiratory tract irritation when inhaled at exposure concentrations below those causing frank respiratory tract corrosion [...] The Category 3 classification would occur only when more severe effects in the respiratory system are not observed." In the CLH report, no severe respiratory effects from OPP were reported for any of the inhalation toxicity studies.

Furthermore, in the renewal assessment report of OPP prepared according to Regulation (EC) No 1107/2009 (Vol. 3, B.6.9.5 "Diagnosis of poisoning"; dated November 2021), the Rapporteur Member

State (also the DS for the CLP evaluation) concluded that OPP and sodium *ortho*-phenylphenate (SOPP) are considered irritant to the respiratory tract. However, the evidence for this conclusion is not clear.

Could the DS provide further elaboration on this classification in light of this comment? Based on the available toxicity data and in accordance with the CLP guidance, we are of the opinion to retain the STOT SE 3 (H335) classification for OPP.

Hazardous to the aquatic environment:

We agree that 2-phenylphenol is considered as rapidly degradable because it is readily degradable based on the screening tests. However, in chapter 2.8.4.1 monitoring data of 2-phenylphenol in surface water were given. Monitoring data should only be used as supporting evidence for demonstration of either persistence in the aquatic environment, or of rapid degradation. Could you please discuss the meaning of the found concentrations? The existence of monitoring data does not support the rapid degradation of 2-phenylphenol.

We agree to the proposed classification as Aquatic Acute 1, M-factor = 1 and Aquatic Chronic 1, M-factor = 1.