Title

Active Substance Mixture Review on Developmental Data for CLP Purposes

Test Item

QRD 420 as it relates to QRD 460

Data Requirement(s) / Guideline(s)

OECD Guidelines for the testing of Chemicals: Test Guideline 414
US EPA OCSPP Guideline OPPTS 870.3700

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Summary

QRD 420 does not meet the classification under CLP as Reproductive Toxicant, Category 2. This classification was proposed on the individual component, alpha-terpinene, due to a significant reduction in the number of pregnant females observed at the high dose level in a non-OECD guideline, non-GLP developmental toxicology study. This effect was only observed in females with significant maternal toxicity exhibiting body weight loss (41.9% body weight gain of control animals) and secondary non-specific consequences on the foetuses (i.e. decreased fetal and litter weight and retarded ossifications).

However, Section 3.7.3.2.1 (Classification of mixtures when data are available for complete mixture), of the CLP classification criteria states:

> "Classification of mixtures will be based on the available test data for the individual ingredients of the mixture using concentration limits for the ingredients of the mixture. ***On a case-by-case basis, test data on mixtures may be used for classification*** when demonstrating effects that have not been established from the evaluation based on the individual components. In such cases, ***the test results for the mixture as a whole must be shown to be conclusive taking into account dose and other factors such as duration, observations, sensitivity and statistical analysis of reproduction test systems. Adequate documentation supporting the classification shall be retained and made available for review upon request***."

The developmental toxicity study conducted on QRD 420 (complete mixture) meets each criteria outlined for evaluation on test data on mixtures, whereas the Araujo et al., (1996) study conducted with alpha-terpinene does not. Additionally, developmental toxicity studies for each of the terpinenes included in QRD 420 are not available for review.

Therefore, classification according to CLP should be applied as stated in Section 3.7.3.2.1 for QRD 420 on the test data on the mixture.

Background

QRD 420, is a terpenoid blend active substance registered in the United States. QRD 420 was patterned after the composition of the original plant extract active substance (Extract of *Chenopodium ambrosioides* near *ambrosioides*), which consisted of approximately 67% of the three terpenes and 33% plant derived impurities. QRD 420 replaced the impurities with canola oil in order to maintain the same proportionality as the plant extract. For the EU submission, canola oil was removed and QRD 460 was registered, which contains only the three terpenes in proportions equivalent to those found in the plant extract and QRD 420.

alpha-Terpinene (1-isopropyl-4-methylcyclohexa-1,3-diene), the subject of reproductive toxicity hazard classification, is a naturally occurring cyclic monoterpene produced in the

secondary metabolism of plants like citrus, peppermint, thyme, basil, and papaya. It has been identified in numerous plant extracts and is present in several commonly used oils, including tea tree oil and may be used in fragrances for soap, detergents, creams/lotions and perfumes as part of natural oils. Due to its anti-oxidant activity, alpha-terpinene is suggested as an agent for maintaining the oxidative stability of different matrices such as food, cosmetics, medicaments, and plant protection products. alpha-Terpinene is listed in the Code of Federal Regulations Title 21 172.515 and EU regulation 872/2012 as a food additive permitted for direct addition to food for human consumption (CFR 2015; EC 2012).

Experimental Data

There are two relevant studies which can be evaluated for reproductive toxicity:

1) A non-GLP, non-guideline study with 89% alpha-terpinene; Araujo et al.(1996)
2) A GLP, OECD 414 guideline study with QRD 420, containing 38.8% alpha-terpinene; [redacted] (2009)

The results of both of the abovementioned studies have been provided and summarized by [redacted], 2011 and [redacted] and [redacted], 2018. Both studies support the conclusion that there is a clear impact of high-dose alpha-terpinene or QRD 420 exposure on maternal health, as indicated by **significantly reduced body weight gain** observed during gestation, according to Section 3.7:

> "Substances are classified in Category 2 for reproductive toxicity when there is some evidence from humans or experimental animals, possibly supplemented with other information, of an adverse effect on sexual function and fertility, or on development, and where the evidence is not sufficiently convincing to place the substance in Category 1. If deficiencies in the study make the quality of evidence less convincing, Category 2 could be the more appropriate classification.
>
> Such effects shall have been observed in the ***absence of other toxic effects***, or if occurring together with other toxic effects the adverse effect on reproduction is considered ***not to be a secondary non-specific consequence of the other toxic effects***."

However, based on the criteria set for the by CLP, Section 3.7.3.2:

> *"On a case-by-case basis, test data on mixtures may be used for classification when demonstrating effects that have not been established from the evaluation based on the individual components. In such cases, the test results for the mixture as a whole must be shown to be conclusive taking into account* ***dose and other factors such as duration, observations, sensitivity and statistical analysis of reproduction test systems. Adequate documentation*** *supporting the classification shall be retained and made available for review upon request."*

A developmental toxicity study does not exist for two of QRD 420 components, and based on our review of the data from Araujo et al., (1996), effects have not been established in the absence of maternal toxicity. Therefore, Bayer evaluated the two available studies based on the CLP criteria to determine if the data generated on QRD 420 would meet the standards set forth for evaluation of the mixture. Table 1 summaries the data generated from the two studies and whether or not the studies meet the requirements of Section 3.7.3.2 of the CLP Classification.

Table 1. Evaluation of Data Generated from 2 Relevant Developmental Toxicity Studies According to Section 3.7.3.2 CLP Criteria for Mixtures Classification

Criteria	QRD420 Study	Comments	Araujo et al. Study	Comments
Test Results Conclusive	√	No developmental effects in the absence of maternal toxicity	√	No developmental effects in the absence of maternal toxicity
Dose	√	Dose Confirmation Provided in Study Report, According to OECD 414 Guidelines		No dose confirmation provided
Duration	√	GD 6-19, According to OECD 414 Guidelines	√	GD 6-15
Observations	√	Recorded, According to OECD 414 Guidelines		Not provided
Sensitivity	√	MTD met, According to OECD 414 Guidelines	√	MTD met
Statistical Analysis	√	According to OECD 414 Guidelines	√	Conducted ANOVA followed by t-test rather than Dunnett's for parametric data
Documentation-retained and available for review	√	GLP study conducted, with retained records available for review		Non-GLP, unknown status of record retention

Based on the requirements of Section 3.7.3.2, the data generated on QRD 420 was GLP-compliant following OECD 414 guidelines and meets all of the requirements for acceptability for review of the data generated on the mixture (Table 1). The Araujo et al. (1996), study did not provide clinical observations, dose confirmation, no indication on specific animals which lost litters, the individual body weights of the dams, and uncertainty exists on whether any records were retained if additional review were required. Furthermore, the statistical approach used (ANOVA followed by t-test) is not a standard approach to analyze multiple dose levels. Therefore, Bayer requests that the data generated on QRD 420 be considered in lieu of alpha-terpinene.

As summarized in [redacted] (2011), there is no experimental evidence for QRD 420 to meet the developmental toxicity classifications. Table 2 summarizes the experimental evidence from the developmental toxicity study on QRD 420.

Additional Considerations

Terpenoid Blend QRD 460 meets the requirements for Annex IV listing. Substances included in Annex IV are exempted from registration for all their possible uses, irrespective of the tonnage in which they are manufactured or imported. Information is known about Annex IV substances that they are considered to cause minimum risk because of their intrinsic properties. Moreover, residues arising from use of the active substance are indistinguishable from natural background levels or other sources substances for which MRLs are not required. Following application of product containing QRD 460, components are expected to quickly decline to natural background levels (EFSA, 2014).

Discussion in relation to classification and labelling – CLH/GHS

There is no evidence of QRD 420 (terpinene blend) causing adverse effects in humans on sexual function, fertility or development; therefore it is proposed that the available animal data are the appropriate basis for potential classification.

In consideration of the classification and labelling criteria (EU CLP regulation 1272/2008, 3.7); no adverse effects on sexual function, fertility, development of the conceptus, lactation or the development of the offspring without exhibiting maternal toxicity occurred (Table 2). It is considered that the weight of the evidence supports that there is sufficient information to conclude there is **no concern for QRD 420 as a Category 2 reproductive toxicant**.

Table 2. Experimental Evidence for QRD 420 to meet Developmental Toxicity Classifications

Categories	Criteria	Experimental Evidence	Conclusion
Category 1A	*Known human reproductive toxicant* The classification of a substance in Category 1A is largely based on evidence from humans.	None	Does not meet criteria for Category 1A
Category 1B	*Presumed human reproductive toxicant* The classification of a substance in Category 1B is largely based on data from animal studies. Such data shall provide clear evidence of an adverse effect on sexual function and fertility or on development in the absence of other toxic effects, or if occurring together with other toxic effects the adverse effect on reproduction is considered not to be a secondary non-specific consequence of other toxic effects. However, when there is mechanistic information that raises doubt about the relevance of the effect for humans, classification in Category 2 may be more appropriate.	None	Does not meet criteria for Category 1B
Category 2	*Suspected human reproductive toxicant* Substances are classified in Category 2 for reproductive toxicity when there is some evidence from humans or experimental animals, possibly supplemented with other information, of an adverse effect on sexual function and fertility, or on development, and where the evidence is not sufficiently convincing to place the substance in Category 1. If deficiencies in the study make the quality of evidence less convincing, Category 2 could be the more appropriate classification. Such effects shall have been observed in the absence of other toxic effects, or if occurring together with other toxic effects the adverse effect on reproduction is considered not to be a secondary non-specific consequence of the other toxic effects.	↓ Maternal BW gain Secondary non-specific consequences of maternal toxicity: • ↓ fetal weights • Delayed ossification	Does not meet criteria for Category 2

Conclusions on Classification and Labelling

According to Section 3.7.3.2.1 (Classification of mixtures when data are available for complete mixture), QRD 420 meets the criteria to use test data on mixtures for classification as a GLP, OECD guideline study on the complete mixture is available for evaluation.

According to Annex VI of Regulation (EC) No 1272/2008, QRD 420 does not meet the criteria for Reproductive Toxicant, Category 2.

References

Araujo IB et al (1996): Study of the Embryofoetotoxicity of α-Terpinene in the Rat: Food and Chemical Toxicology 34, p477-482.

CFR (2015), 'Code of Federal Regulations Title 21', http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?fr=172.515

EC, The European Commission (2012), 'COMMISSION IMPLEMENTING REGULATION (EU) No 872/2012.

EC, The European Commission (2008), No 1272/2008 of the European Parliament and of the Council of 16 December 2008 on classification, labelling and packaging of substances and mixtures, amending and repealing Directives 67/548/EEC and 1999/45/EC, and amending Regulation (EC) No 1907/2006.

[redacted] (2009) A Developmental Toxicity Study of Orally Administered QRD 420 in Rats. IITRI Project Number 2212-001, M-459950-001-1.

[redacted] (2011) REVIEW OF THE EFFECTS OF α-TERPINENE IN THE PREGNANT RAT. Regulatory Science Associates.

[redacted] and [redacted] (2018). alpha-Terpinene: Developmental Data Review for CLP Purposes.