EUROPEAN CHEMICALS AGENCY
BOARD OF APPEAL

SUMMARY OF THE DECISION OF 9 APRIL 2024 OF THE BOARD OF APPEAL OF THE EUROPEAN CHEMICALS AGENCY

Case A-008-2022

(Substance evaluation – Mutagenicity – Error of assessment – Principle of proportionality – Principle of the protection of legitimate expectations – Article 25 – Duty to state reasons)

Factual background

The appeal concerned a decision on the substance evaluation of 5-amino-o-cresol[1].

On 24 May 2022, the Agency adopted the Contested Decision requesting the Appellant and other registrants of the Substance, to provide information on an *in vivo* mammalian alkaline comet assay (OECD TG 489) in liver, gastro-intestinal tract (glandular stomach and duodenum) and urinary bladder performed in rats via the oral route using the Substance. The *in vivo* comet assay was requested to investigate a concern related to mutagenicity – both chromosomal aberration and gene mutation.

The Appellant requested the Board of Appeal to annul the Contested Decision.

Main findings

- *Concern related to chromosomal aberration*

The Appellant's registration dossier contains information on *in vitro* studies which, on their own, indicate a potential hazard related to chromosomal aberration. To investigate those findings, the Appellant's dossier contains, amongst other information, the results of two micronucleus tests performed in 2002 and 2005 respectively according to OECD TG 474.

According to the Contested Decision, the results of the 2005 micronucleus test are inconclusive because of insufficient exposure of the Substance to bone marrow and a lack of investigation of effects at the first site of contact.

However, the Board of Appeal found that the Agency committed an error in concluding that the results of the 2005 micronucleus test were inconclusive, rather than clearly negative as reported in the robust study summary. The Board of Appeal noted that under OECD TG 474 there is no threshold for bone marrow exposure. Furthermore, it was clear from the available evidence that there was systemic exposure, and therefore bone marrow exposure, to the Substance in the 2005 micronucleus test.

The Board of Appeal also noted that OECD TG 474 does not require an examination of the first site of contact. Although under substance evaluation the Agency may require additional information to examine a concern related to the first site of contact, the Agency failed to demonstrate that such an examination was necessary in the present case.

In the absence of other results to the contrary, a negative result in a well-performed micronucleus test, such as the 2005 micronucleus test, is sufficient to exclude a concern related to chromosomal aberration.

[1] EC No 220-618-6; CAS No 2835-95-2 (the '**Substance**').

The Board of Appeal also found that, because of the mode of administration used, the negative results of the 2002 micronucleus test were not, on their own, sufficient to clarify the potential risk related to chromosomal aberration. However, the results of that test do not contradict or call into question the negative results of the 2005 micronucleus test. Consequently, the results of the 2002 micronucleus test cannot affect the conclusion drawn from the 2005 micronucleus test that the Substance does not constitute a potential risk related chromosomal aberration.

The Board of Appeal therefore concluded that the Agency breached the principle of proportionality by failing to demonstrate that the requested information is necessary in order to investigate a potential risk related to chromosomal aberration. The Contested Decision was therefore annulled in so far as it concludes that there is a concern related to chromosomal aberration.

- *Concern related to gene mutation*

The Appellant's registration dossier contains information on *in vitro* studies which, on their own, indicate a concern related to gene mutation. To investigate the findings of the *in vitro* studies, the Appellant's dossier contains, amongst other information, the results of an *in vivo* comet assay conducted in 2005 and a UDS assay performed according to OECD TG 486. The Appellant also submitted to the Agency an opinion of the Scientific Committee on Consumer Products and an expert statement.

The Board of Appeal decided that the Appellant did not demonstrate that, even when the available evidence is taken together, the Agency committed an error in finding that there is a potential risk related to gene mutation.

The Board of Appeal noted that, contrary to the Appellant's arguments, the results of the 2005 comet assay were not capable of clarifying the results of the *in vitro* studies due to deficiencies in the conduct of that study. In addition, as acknowledged in the Agency's guidance documents and OECD TG 486, the negative results of the UDS assay contained in the Appellant's registration dossier are not sufficient, on their own, to clarify the remaining concern related to gene mutation in the liver.

The concern related to gene mutation was also not clarified by the other information available in the Appellant's registration dossier and submitted during the substance evaluation process, even where all that information was taken together.

The Appellant also failed to demonstrate that the Agency committed an error in concluding that there is a need to clarify the potential risk related to gene mutation and that the requested information has a realistic possibility of leading to improved risk management measures.

The Appellant's pleas that the Agency breached the principle of the protection of legitimate expectations, Article 25 and the duty to state reasons were also rejected. The appeal was therefore dismissed in so far as it related to the concern related to gene mutation.

Result

The Board of Appeal annulled the Contested Decision with regard to the concern related to chromosomal aberration and dismissed the appeal with regard to the concern related to gene mutation.

The Board of Appeal noted that the parts of the Contested Decision regarding the concerns related to chromosomal aberration and gene mutation are clearly severable. As a result, the Board of Appeal would have been competent, under Article 93(3) of the REACH Regulation, to replace the Contested Decision with a decision seeking to clarify the concern related to gene mutation only.

However, before replacing a substance evaluation decision with its own decision, the Board of Appeal must examine whether the available evidence allows it to do so. It must also take into account the procedure for adopting Agency decisions under the substance evaluation process, and in particular the role of the various actors in that procedure.

The Agency requested the *in vivo* comet assay in the Contested Decision because, amongst other reasons, it considered that that test is the most appropriate to clarify the concerns related to both chromosomal aberration and gene mutation.

The most appropriate and least onerous test to address the concern related only to gene mutation was not discussed during the decision-making procedure in the present case. Therefore, the relevant actors were not given the opportunity to comment on this issue. Consequently, the Board of Appeal did not possess sufficient information to be able to decide whether the comet assay (OECD TG 489), or another test, is the most appropriate test in the present case.

Therefore, the Board of Appeal decided that the case must be remitted to the Agency for further action.
