Committee for Risk Assessment

RAC

Annex 2

Response to comments document (RCOM)

to the Opinion proposing harmonised classification and labelling at EU level of

Barium chromate

EC Number: 233-660-5
CAS Number: 10294-40-3

CLH-O-0000007322-81-01/F

Adopted

8 June 2023

ANNEX 2 - COMMENTS AND RESPONSE TO COMMENTS ON CLH PROPOSAL ON BARIUM CHROMATE

COMMENTS AND RESPONSE TO COMMENTS ON CLH: PROPOSAL AND JUSTIFICATION

Comments provided during consultation are made available in the table below as submitted through the web form. Any attachments received are referred to in this table and listed underneath, or have been copied directly into the table.

All comments and attachments including confidential information received during the consultation have been provided in full to the dossier submitter (Member State Competent Authority), the Committees and to the European Commission. Non-confidential attachments that have not been copied into the table directly are published after the consultation and are also published together with the opinion (after adoption) on ECHA's website. Dossier submitters who are manufacturers, importers or downstream users, will only receive the comments and non-confidential attachments, and not the confidential information received from other parties. Journal articles are not confidential; however they are not published on the website due to Intellectual Property Rights.

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Substance name: Barium chromate
EC number: 233-660-5
CAS number: 10294-40-3
Dossier submitter: The Netherlands

GENERAL COMMENTS

Date	Country	Organisation	Type of Organisation	Comment number
01.09.2022	France		MemberState	1
Comment received				
FR agrees with this interesting read-across approach. We support the choice of zinc chromate and zinc tetrahydroxy chromate for read-across because of the similar water solubility and similar mutagenic effects to barium chromate.				
Dossier Submitter's Response				
Thank you for your support of the chosen approach.				
RAC's response				
Thank you for your comment. Scientific Committee on Occupational Exposure LimitsRAC agrees with the read-across of barium chromate to zinc chromate and zinc tetrahydroxy chromate as proposed by the DS.				

Date	Country	Organisation	Type of Organisation	Comment number
23.08.2022	Germany		MemberState	2
Comment received				
The proposed classification is based on read across to other chromium(VI) compounds, in this case mainly to other poorly soluble substances such as zinc chromate and zinc tetrahydroxychromate. It is recommended not to restrict read-across to poorly soluble chromium(VI) compounds.				
Dossier Submitter's Response				
Thank you for your comment. We would like to address it together with your other comments below.				
RAC's response				
Noted.				

CARCINOGENICITY

Date	Country	Organisation	Type of Organisation	Comment number
01.09.2022	France		MemberState	3

Comment received

FR supports the classification proposal of barium chromate as, at least, Carc. 1B, H350 and agrees with the rationale based on the harmonized classification Carc. 1A of zinc chromate and zinc tetrahydroxy chromate.

It is written p35/36 : " However, in the absence of meaningful epidemiologic data for barium chromate no classification as Category 1A carcinogen is suggested. No classification of barium chromate as Category 1A carcinogen is consistent with the classification of lead chromate (classified as Category 1B carcinogen). Workers active in the production of chromate pigments were often exposed to both, zinc and lead chromate. However, subgroup C of the study of Davies (1984), which was only exposed to lead chromate, did not show an increased tumour incidence, whereas the other subgroups A and B, which were exposed to zinc and lead chromate, clearly showed an increased lung cancer incidence. An observation also supported by other epidemiologic data. Based on these observations a classification of barium chromate as carcinogen category 1A without clear evidence from epidemiological data does not seem to be appropriate. "

We would like to know if you considered the role of the barium atom in the toxicity of barium chromate. Does barium have properties that are closer to zinc or lead? If its properties are closer to zinc, in our opinion, this could direct the discussion towards a carc.1A classification.

Dossier Submitter's Response

We thank you for your support for the classification proposal.

The carcinogenicity of chromates is related to the biological activity of the Cr(VI) moiety. The underlying mode of action as described in section 10.1 of the CLH report is well understood. The contribution of the cation is expected to be small, mainly influencing the solubility and bioavailability of the anion. There is no evidence, e.g. from carcinogenicity studies with barium chloride, that the barium cation itself has carcinogenic properties. The water solubility of barium chromate is also close to that of lead chromate (a substance classified 1B). However, as the lead cation has a strong toxicity on its own and lead compounds other than lead chromate show some carcinogenic activity, read across to lead chromate is not without difficulties. Therefore, read-across to zinc chromates was preferred. Zinc chromates are classified Carc 1A, however, the epidemiological evidence underlying this classification has some weaknesses (as described in the dossier). In conclusion, there are arguments for both classifying Carc 1A (with direct reference to the classification of the read-across substances zinc chromates) and for Carc 1B. With the evidence for the zinc chromates **and** giving consideration to the known activity of the chromate ion as such, the evidence from genotoxicity studies, however also taking into account the limitations of the overall database we concluded Carc 1B to more adequately summarise the overall evidence.

RAC's response

RAC supports the DS's reasoning and agrees with Carc. 1B classification for barium chromate.

Date	Country	Organisation	Type of Organisation	Comment number
23.08.2022	Germany		MemberState	4

Comment received

Classification of barium chromate as Carc. 1B is supported.
Barium chromate is one of the poorly soluble chromium(VI) compounds. Chromium(VI) is a epidemiologically proven human carcinogen with very high potency. It can be assumed that even a few chromium(VI) ions released due to the poor solubility of barium chromate can lead to a carcinogenic effect.

Since there are no suitable studies on the carcinogenicity of barium chromate, a read-across to zinc chromates was proposed in the CLH proposal based on solubility aspects: as barium chromate is considered as a substance of low solubility, zinc chromate and zinc tetrahydroxychromate, which also exhibit low water solubility compared to other chromium salts, are used as read-across substances.

The underlying hypothesis in the dossier is that solubility is considered a key element in the toxic effects of the source and target compounds, i.e. formation of chromium (Cr) VI anions, uptake of Cr(VI) anions into cells followed by intracellular reduction to Cr(III). Here we wonder why so much focus of the argumentation is placed on the aspect of solubility as it has been described that Cr(VI) compounds might also enter the cells in particulate form (e.g. endocytosis, phagocytosis) which should be considered in the argumentation. Furthermore, also particle size needs to be considered when discussing cellular uptake.

Then, apart from solubility, the question would be whether barium chromate is able to enter the cells. This has been demonstrated in vitro in WTHBF-6 cells. The positive in vitro tests on the mutagenicity of barium chromate suggest that Cr(VI) can reach the cells and thus have a genotoxic effect. Another aspect to consider is whether barium chromate becomes systemically available by one of the relevant uptake routes (inhalation, oral, dermal). Although the toxicokinetic studies performed with barium chromate lack proper documentation and were not performed according to modern standards, systemic bioavailability could be demonstrated in rats and mice after inhalation exposure.

Thus, it can be assumed that barium chromate can be taken up systemically and into cells. Here we wonder why not a broader, more holistic view on chromate compounds in general is taken into consideration, i.e. that after cellular uptake in principle the same qualitative events can take place as for other Cr(VI) compounds. Argumentation in this regard was supported by Hartwig (2012):
"As a result of the higher solubility of barium chromate, better absorption and bioavailability compared with that of lead chromate can be assumed. After being taken up by phagocytosis into the cell, the chromium(VI) is then reduced to chromium(III) via the reactive intermediate forms chromium(V) and chromium(IV). Radical oxygen and sulphur compounds are formed during this process, and in the cell nucleus chromium (III)–DNA adducts, and DNA–protein and DNA–DNA crosslinks occur. Chromium–DNA adducts can reduce the accuracy of base pair formation during DNA replication, cause gene mutations and lead to the formation of DNA double strand breaks and as a consequence to chromosome breaks and the formation of micronuclei. As a result of the same mechanism of action and the chromium–DNA adducts and chromosomal aberrations caused also by barium chromate carcinogenic effects are suspected also for barium chromate. This means that all chromium(VI) compounds must be considered as carcinogenic in humans….".
Therefore, in Germany, according to TRGS 910, all Cr(VI) compounds are considered

together.

For the evaluation of carcinogenicity, five studies were considered in which barium chromate was administered to rats via non-physiological routes such as intrapleural, intrabronchial and intramuscular application. None of these rather old studies is reliable from a current point of view, as they were not carried out according to test guidelines and important data such as sex, body weight, or survival rates of the animals are missing. Also, from the few descriptions of the studies, it is not possible to conclude on the actual dose of barium chromate to which the animals were exposed. In four of the five studies, no tumours were found. In one of the five studies, a tumour was found, but since this was found at the implantation site, it adds limited weight to the evidence for a carcinogenic potential of the substance.

To evaluate the carcinogenicity of barium chromate, studies were included that were carried out with the read-across substances zinc chromate and zinc tetrahydroxychromate. However, these studies also have weaknesses, as non-physiological routes were chosen, in which the substances were administered via intrabronchial application. These studies are also quite old and have not been conducted according to test guidelines. In the studies with zinc tetrahydroxychromate after intrabronchial application, one tumour was found in 100 rats and with zinc chromate after pellet implantation three and five tumours were found in 100 rats, respectively. These studies also lack information on the exact dose to which the animals were exposed. Here, a comparison with studies with soluble chromium compounds could be used, in which the substances were administered, for example, via oral application.

Nevertheless as mentioned in the beginning: (1) despite low solubility barium chromate has been shown to be capable of entering cells, (2) systemic availability of Cr species has been demonstrated in vivo after inhalation exposure in rats and mice, and (3), in principle, qualitatively the same intracellular mechanisms can take place as observed for other Cr(VI) compounds, Therefore, the classification proposal in favour of category 1B for carcinogenicity can be supported.

In the dossier, the classification proposal for barium chromate is justified with a read-across to the zinc chromates. It would be appreciated if this was presented in more detail. The bioavailability of Cr(VI) from poorly soluble chromium compounds is recommended to be discussed more thoroughly. For the justification of the classification proposal of barium chromate, the human epidemiology Cr(VI) could also be addressed.

References:
https://www.baua.de/DE/Angebote/Rechtstexte-und-Technische-Regeln/Regelwerk/TRGS/Begruendungen-910.html

Hartwig, A.; MAK Commission (2012) Chrom(VI) -Verbindungen (einatembare Fraktion) [MAK value documentation in German language] Loseblattsammlung, 53. Lfg. DFG Deutsche Forschungsgemeinschaft, WILEY-VCH Verlag Weinheim

Dossier Submitter's Response

Thank you for your comments.
We agree with the commentator that in principle all Cr(VI) compounds are suspected to be carcinogenic due to their known mechanism of action. Based on the data available for the different compounds, there are harmonised classifications for some substances in Cat. 1A and for others in Cat. 1B. The particular difficulty with barium chromate is that there are no qualified animal studies and especially no qualified epidemiological studies. For the

justification document, therefore, the way chosen was to evaluate by RA to substances with comparable solubility.
In your comment you argue that data exist which show the principle intracellular availability of the chromate ion from barium chromate. We agree with this conclusion from the data as described in the dossier in section 10.2. And we used it to corroborate our conclusion that read-across to other poorly soluble chromates is justified. However, we consider the quantitative difference in bioavailability between barium chromate and soluble chromates such as sodium dichromate so large that a qualitative comparison with these substances can be challenged (e.g. Miyai and colleagues described quantitative differences in tissue concentrations and half lives for barium chromate and sodium chromate, see dossier, section 10.2, which possibly might influence the effects).
You further mention that other studies show phagocytosis as another, important pathway of cellular uptake of barium chromate and conclude that solubility should not be given such weight. However, to our knowledge, limited evidence is available to conclude that phagocytosis is a quantitatively relevant uptake mechanisms for barium chromate in target cells: None of the publications cited by Hartwig or cited in the secondary literature referred to by Hartwig actually investigated uptake of barium chromate by phagocytosis (only other chromates). These publications address phagocytosis by lung macrophages after the administration of sodium dichromate or metallic chromium. In the recommendation of the Scientific Committee on Occupational Exposure Limits for lead chromate (SCOEL/SUM/117M March 2004) two publications are cited which observed the intracellular uptake of lead chromate particles by phagocytosis in cultivated somatic cells. But at the same time, the SCOEL recommendation also pointed out that, in addition to phagocytosis, solubility also played an important role in the observed effect. ("*these data were interpreted to show that although phagocytic particle uptake occurs, particle-cell contact and extracellular dissolution were decisive factors for the clastogenic activity of lead chromate*").
Therefore, the available data on phagocytotic uptake do not convincingly show that intracellular chromate levels can be expected for barium chromate to assume a qualitative similar situation with soluble chromates. To encounter respective criticisms and with explicit consideration given to the data for barium chromate showing some bioavailability and the generally acknowledged carcinogenic properties of the Cr(VI) moiety we restricted the read-across approach to less soluble chromates. Nevertheless, we do not contradict your conclusion that all chromates are likely carcinogens, but just consider the comparison with chromates with similar physico-chemical properties more adequate.

With regard to your final suggestions, we would like to point out the following:
We have tried to take into account all available data for the read-across, especially, toxicokinetic data and data on other toxicological endpoints were checked for the source and target substances for a valid comparison. However, the limited data on barium chromate and zinc chromate does not allow to extend the read-across arguments beyond the rationale already documented in the CLH report. We have reported all available data on barium chromate and the associated data on zinc chromate. The same holds true for the epidemiological data: the available limited epidemiological data for zinc and barium chromate are already presented in the dossier.

RAC's response

RAC supports the DS's response. The read-across of barium chromate to zinc chromate and zinc tetrahydroxy chromate that has similar water solubility is adequate for the proposed classification.

MUTAGENICITY

Date	Country	Organisation	Type of Organisation	Comment number
01.09.2022	France		MemberState	5
Comment received				
FR agrees that the information available does not allow to propose a classification for mutagenicity for barium chromate. The substance cannot be classified based on unconclusive data.				
Dossier Submitter's Response				
Thank you for your support of the chosen approach.				
RAC's response				
Noted.				