CLH report

Proposal for Harmonised Classification and Labelling

**Based on Regulation (EC) No 1272/2008 (CLP Regulation),
Annex VI, Part 2**

Chemical name: Barium Chromate

EC Number: 233-660-5

CAS Number: 10294-40-3

Index Number: --

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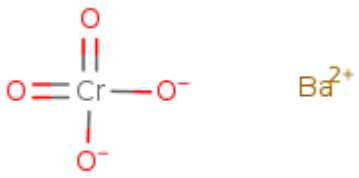
CONTENTS

1 IDENTITY OF THE SUBSTANCE

1.1 Name and other identifiers of the substance

Table 1: Substance identity and information related to molecular and structural formula of the substance

Name(s) in the IUPAC nomenclature or other international chemical name(s)	Barium chromate
Other names (usual name, trade name, abbreviation)	-
ISO common name (if available and appropriate)	-
EC number (if available and appropriate)	233-660-5
EC name (if available and appropriate)	Barium chromate
CAS number (if available)	10294-40-3
Other identity code (if available)	-
Molecular formula	$BaCrO_4$
Structural formula	
SMILES notation (if available)	[Ba++].[O-][Cr]([O-])(=O)=O
Molecular weight or molecular weight range	253.37 g/mol
Information on optical activity and typical ratio of (stereo) isomers (if applicable and appropriate)	Not relevant
Description of the manufacturing process and identity of the source (for UVCB substances only)	Not relevant
Degree of purity (%) (if relevant for the entry in Annex VI)	Not relevant

1.2 Composition of the substance

Table 2: Constituents (non-confidential information)

Constituent (Name and numerical identifier)	Concentration range (% w/w minimum and maximum in multi-constituent substances)	Current CLH in Annex VI Table 3 (CLP)	Current self-classification and labelling of registrant*
Barium chromate CAS No. 10294-40-3 EC No. 233-660-5	Confidential information, see confidential Annex	No harmonised classification available	Acute Tox. 3, H301 Acute Tox. 3, H311 Acute Tox. 2, H330 Resp. Sens. 1, H334 Skin Sens. 1, H317 Repr. 2, H361 Muta. 1B, H340 Carc. 1A, H350 STOT RE 1, H372 Aquatic Acute 1, H400 Aquatic Chronic 1, H410

* ECHA Dissemination (2021), Information on Chemicals - Registered Substances, European Chemicals Agency. Online: http://echa.europa.eu/web/guest/information-on-chemicals/registered-substances; accessed 23 August 2021

Barium chromate is a mono-constituent substance (CAS number: 10294-40-3). The current self-classification by the registrants is given in Table 2. The frequency of hazard classifications among all notifications provided to the ECHA C&L Inventory was retrieved from PubChem on 21/10/2021 and is given below. In total, 487 companies provided notifications with hazard classifications (22 aggregated notifications).

Hazard classifications occurring in at least 10% of notifications:

Hazard code	Hazard statement	% of notifications
H272	May intensify fire; oxidizer	15.61
H301	Toxic if swallowed	19.3
H302	Harmful if swallowed	76.18
H317	May cause an allergic skin reaction	17.25
H332	Harmful if inhaled	91.79
H350	May cause cancer	14.78
H400	Very toxic to aquatic life	12.32
H402	Very toxic to aquatic life with long lasting effects	14.58

Table 3: Impurities (non-confidential information) if relevant for the classification of the substance

Impurity (Name and numerical identifier)	Concentration range (% w/w minimum and maximum)	Current CLH in Annex VI Table 3 (CLP)	Current self-classification and labelling (CLP)	The impurity contributes to the classification and labelling
Confidential information, see confidential Annex.				

Table 4: Additives (non-confidential information) if relevant for the classification of the substance

Additive (Name and numerical identifier)	Function	Concentration range (% w/w minimum and maximum)	Current CLH in Annex VI Table 3 (CLP)	Current self-classification and labelling (CLP)	The additive contributes to the classification and labelling
The substance does not contain additives.					

2 PROPOSED HARMONISED CLASSIFICATION AND LABELLING

2.1 Proposed harmonised classification and labelling according to the CLP criteria

Table 5: Proposed harmonised classification and labelling according to the CLP criteria

	Index No	Chemical name	EC No	CAS No	Classification		Labelling			Specific Conc. Limits, M-factors and ATEs	Notes
					Hazard Class and Category Code(s)	Hazard statement Code(s)	Pictogram, Signal Word Code(s)	Hazard statement Code(s)	Suppl. Hazard statement Code(s)		
Current Annex VI entry	No current Annex VI entry										
Dossier submitter's proposal	TBD	Barium chromate	233-660-5	10294-40-3	Carc. 1B	H350	GHS08 Dgr	H350		-	
Resulting Annex VI entry if agreed by RAC and COM	TBD	Barium chromate	233-660-5	10294-40-3	Carc. 1B	H350	GHS08 Dgr	H350		-	

Table 6: Reason for not proposing harmonised classification and status under consultation

Hazard class	Reason for no classification	Within the scope of consultation
Explosives	hazard class not assessed in this dossier	No
Flammable gases (including chemically unstable gases)	hazard class not assessed in this dossier	No
Oxidising gases	hazard class not assessed in this dossier	No
Gases under pressure	hazard class not assessed in this dossier	No
Flammable liquids	hazard class not assessed in this dossier	No
Flammable solids	hazard class not assessed in this dossier	No
Self-reactive substances	hazard class not assessed in this dossier	No
Pyrophoric liquids	hazard class not assessed in this dossier	No
Pyrophoric solids	hazard class not assessed in this dossier	No
Self-heating substances	hazard class not assessed in this dossier	No
Substances which in contact with water emit flammable gases	hazard class not assessed in this dossier	No
Oxidising liquids	hazard class not assessed in this dossier	No
Oxidising solids	hazard class not assessed in this dossier	No
Organic peroxides	hazard class not assessed in this dossier	No
Corrosive to metals	hazard class not assessed in this dossier	No
Acute toxicity via oral route	hazard class not assessed in this dossier	No
Acute toxicity via dermal route	hazard class not assessed in this dossier	No
Acute toxicity via inhalation route	hazard class not assessed in this dossier	No
Skin corrosion/irritation	hazard class not assessed in this dossier	No
Serious eye damage/eye irritation	hazard class not assessed in this dossier	No
Respiratory sensitisation	hazard class not assessed in this dossier	No
Skin sensitisation	hazard class not assessed in this dossier	No
Germ cell mutagenicity	data lacking	Yes
Carcinogenicity	harmonised classification proposed	Yes
Reproductive toxicity	data lacking	Yes
Specific target organ toxicity-single exposure	hazard class not assessed in this dossier	No
Specific target organ toxicity-repeated exposure	hazard class not assessed in this dossier	No
Aspiration hazard	hazard class not assessed in this dossier	No
Hazardous to the aquatic environment	hazard class not assessed in this dossier	No
Hazardous to the ozone layer	hazard class not assessed in this dossier	No

3 HISTORY OF THE PREVIOUS CLASSIFICATION AND LABELLING

There is no harmonised classification and labelling available for barium chromate. The substance has been included in former activities on harmonised classification as it was exempted from the current group

classification. As documented in Table 3 of Annex VI of the CLP regulation other chromium (VI) compounds (chromium (VI) compounds, with the exception of barium chromate and of compounds specified elsewhere in this Annex; entry 024-017-00-8) have been classified as Carc. 1B (H350i), or as Carc. 1A (zinc chromates including zinc potassium chromate; entry 024-007-00-3).

4 JUSTIFICATION THAT ACTION IS NEEDED AT COMMUNITY LEVEL

There is no requirement for justification that action is needed at Community level. The substance is suspected of having CMR properties (carcinogenicity).

5 IDENTIFIED USES

IARC (1990) reports the following uses for barium chromate: in pyrotechnics, in high-temperature batteries, safety matches, use as a corrosion inhibitor in metal-joining compounds, as a pigment in paints, in ceramics, in fuses, in metal primers, and in ignition control devices. It is also indicated that in Japan the use of barium chromate in explosive fuses has been reported (IARC, 1990). According to ECHA's disseminated database (ECHA Dissemination, 2021) the substance is used by professional workers (widespread uses), in formulation or re-packing, at industrial sites and in manufacturing. The substance is used at industrial sites in coating products, adhesives and sealants, pH regulators and water treatment products and laboratory chemicals.

6 DATA SOURCES

Systematic searches for publications and other relevant data were performed based on the following databases:

- U.S. National Library of Medicine, Pubmed.gov
- TOXNET, ChemIDplus, IPCS, eChemPortal
- Medline, SciSearch, Biosis, PQscitech, Chemical Abstracts (HCA), Embase (at host STN International)

The REACH registration dossier for barium chromate (last modified: 21 January 2019), publicly available from ECHA's disseminated database (ECHA Dissemination, 2021), has been analysed for study references, which then have been considered as data sources for this CLH report. Additionally, the confidential registration dossier was available for evaluation.

Further, the following reviews with toxicological risk assessments on barium chromate and other chromates were used:

- IARC (1990)
- IARC (2012)
- Hartwig and MAK Commission (2012)
- ATSDR (2012)
- SCOEL (2017)
- NIOSH (2008; 2013)
- HCN (2016)

7 PHYSICOCHEMICAL PROPERTIES

Table 7: Summary of physicochemical properties

Property	Value	Reference	Comment (e.g. measured or estimated)
Physical state at 20°C and 101.3 kPa	solid	ECHA Dissemination (2021)	
Melting/freezing point	Substance decomposes at 1400°C	ECHA Dissemination (2021)	Data from secondary literature
Boiling point	-	ECHA Dissemination (2021)	Registration dossier: the study does not need to be conducted because the substance is a solid which melts above 300°C
Relative density	4.498	ECHA Dissemination (2021)	Data from secondary literature
Vapour pressure	-	ECHA Dissemination (2021)	Registration dossier: the study does not need to be conducted because the substance is a solid which melts above 300°C
Surface tension	-	ECHA Dissemination (2021)	Registration dossier: the study does not need to be conducted because surface activity is not a desired property of the material
Water solubility	0.003 g/L at 20°C	ECHA Dissemination (2021)	Data from secondary literature
Partition coefficient n-octanol/water	-	ECHA Dissemination (2021)	Registration dossier: the study does not need to be conducted because the substance is inorganic
Flash point	-	ECHA Dissemination (2021)	Registration dossier: the study does not need to be conducted because the substance is inorganic
Flammability	-	ECHA Dissemination (2021)	Registration dossier: the study does not need to be conducted because the substance is a solid; the study does not need to be conducted because the substance is known to be stable in contact with air at room temperature for prolonged periods of time (days) and hence, the classification procedure does not need to be applied

Property	Value	Reference	Comment (e.g. measured or estimated)
Explosive properties	-	ECHA Dissemination (2021)	Registration dossier: the study does not need to be conducted because there are no chemical groups present in the molecule which are associated with explosive properties
Self-ignition temperature	No data	ECHA Dissemination (2021)	
Oxidising properties	Non-oxidising	ECHA Dissemination (2021)	measured
Granulometry	D10: 1.1 µm D50: 3.2 µm D90: 7.4 µm	ECHA Dissemination (2021)	measured
Stability in organic solvents and identity of relevant degradation products	No data	ECHA Dissemination (2021)	
Dissociation constant	No data	ECHA Dissemination (2021)	
Viscosity	No data	ECHA Dissemination (2021)	

8 EVALUATION OF PHYSICAL HAZARDS

Evaluation not performed for this substance.

9 TOXICOKINETICS (ABSORPTION, METABOLISM, DISTRIBUTION AND ELIMINATION)

Information on toxicokinetic behaviour of barium chromate is only available from two Japanese publications, for which English summaries, tables and figures are available: Miyai (1980) exposed rats and mice towards two different concentrations of barium chromate dust for 6 h/d on 5 to 6 d/w for 15 months. Concentrations were given as 0.1 and 1.0 mg CrO_3/m^3. Based on a molecular mass of 99.99 g/mol for CrO_3 and 253.37 g/mol for $BaCrO_4$ these concentrations correspond to 0.001 and 0.01 mmol/m^3 or 0.25 and 2.5 mg $BaCrO_4$/ m^3. No results for mice were reported in the English summary. In rats, highest chromium concentrations were measured in the lung after barium chromate exposure. The author calculated a biological “halftime” of about 195 days for barium chromate in the lung (22 days for sodium chromate, which was tested in parallel; it is not clear from the summary whether this refers to the residence time of the barium chromate in the lung). In rats, which received 1.0 mg CrO_3/m^3 (for 3 or 6 months, not clearly described in the summary) the chromium concentration increased 677-fold in lung, 50-fold in kidney, 10- to 25-fold in spleen and testis. Chromium concentrations were still increased 30 days after the 15 months inhalation period in the 0.1 mg CrO_3/m^3 barium chromate group (5- to 10-fold in lung and salivary gland; 2.5-5-fold in testis and duodenum) and the 1.0 mg CrO_3/m^3 barium chromate group (792-fold in lung, 25- to 50-fold in stomach and testis, 10- to 25-fold in spleen and brain). No further information was provided in the English summary.

Miyai et al. (1980) reported results of investigations with radioactively labelled barium chromate in mice after "inhalation" (Throughout the summary and in the legends to the illustration "intratracheal injection" is also mentioned. It is not clear if both administration forms were used. In the following paragraph the wording of the English summary is used.). Within 48 hours after intratracheal administration (no further details on dose provided in the English summary) about 88% of the dose remained in the lung. Chromium retention in the whole body of mice was only slightly higher, about 92% of the dose. No (or only minimal amounts of) radioactivity was detected in liver, kidney and blood (data read from figure). Within 17 days after 30 min inhalation (no details on concentration provided in the English summary) the pulmonary absorption rate of barium chromate was "low" (lower than that of sodium or calcium chromate; no quantitative information provided). Urinary excretion (ca. 6% of administered dose) of chromium after intratracheal injection of barium chromate was lower than excretion in faeces (ca. 7.5% of administered dose). In contrast, for calcium chromate a higher urinary (ca. 32% of dose) than faecal excretion (ca. 18% of dose) was observed. Miyai et al. (1980) calculated a biological "half time" of 18 days for barium chromate (7.5 days for sodium chromate). It remains unclear what are the reasons for the substantial difference in the "half time" of barium chromate in rats (195 days) and mice (18.5 days).

10 READ-ACROSS JUSTIFICATION

10.1 Mode of action and read-across hypothesis

Barium chromate is a chromium (VI) compound and therefore it is suspected of being carcinogenic, mutagenic and a reproductive toxicant. However, studies with barium chromate on CMR endpoints are sparse. Some non-guideline studies investigating mutagenicity *in vitro* and carcinogenicity *in vivo* have been identified (for details see sections 11.8 and 11.9, respectively). The quality of these data is insufficient to base a justification for a harmonised classification on them. No studies with barium chromate on reproductive toxicity are available, neither for effects on fertility nor for effects on development. Additionally, there are no epidemiologic data available for barium chromate.

Therefore, a classification of barium chromate for carcinogenicity based on read-across to other chromium (VI) compounds is proposed. In the absence of any data on reproductive effects of barium chromate no classification for reproductive toxicity will be proposed. For the read-across, information from Cr(VI) substances with harmonised classification will be considered. Harmonised classifications are available for different chromium (VI) compounds, for example for the soluble sodium and potassium dichromate (index no. 024-004-00-7 and 024-002-00-6, respectively), chromium trioxide (index no. 024-001-00-0) as well as for less soluble compounds like zinc chromates including zinc potassium chromate (index no. 024-007-00-3), lead chromate (index no. 082-004-00-2) and strontium chromate (index no. 024-009-00-4). The group entry "zinc chromates including zinc potassium chromate", classified Carc. 1A, comprises several substances, among them zinc chromate (CAS 13530-65-9) and zinc chromate oxide ($Zn_2(CrO_4)O$), monohydrate (CAS 15930-94-6, also called zinc tetrahydroxy chromate or basic zinc chromate), for which genotoxicity and epidemiological data exist. A complete list of substances included in this group is not available.

The read-across is based on poorly soluble substances, as it is assumed that the water solubility of the substances has a relevant influence on their bioavailability. Therefore, substances with similar water solubility as barium chromate have been selected (see below).

A read-across from other Cr(VI) substances to barium chromate is based on the hypothesis that the Cr(VI) component of the substance, the chromate anion, reaches the target cells and elicits its toxic effects following the same mechanism of action (MoA). The following mechanism(s) of action for carcinogenicity and mutagenicity is discussed: Cr(VI) anions, which are structurally similar to sulphate and phosphate, enter the target cells via anion transporters. If Cr(VI) anions are extracellularly reduced to Cr(III) prior to transport via the cell membrane, the Cr(III) ions are not absorbed via anion transporters and are therefore of limited toxicity. Once inside the cells Cr(VI) is reduced to Cr(III). DNA damage can occur either by direct binding of Cr(III) to DNA and/or proteins and/or by reactive oxygen species generated during the reduction of Cr(VI) and may subsequently give rise to mutations. Additionally, cell proliferation/hyperplasia is observed after Cr(VI) exposure through which the mutation can spread and cancer can develop (ATSDR, 2012; Hartwig, 2012; Health Canada, 2016). Besides a direct-acting mutagenic MoA, another MoA is discussed: As described

before, Cr(VI) anions enter the cells via anion transporters and are reduced intracellularly. This might cause oxidative stress and cytotoxicity which is followed by hyperplasia as regenerative response, which might be accompanied by an increased rate of spontaneous mutations. The latter MoA is especially discussed in the context of gastrointestinal cancer after Cr(VI) exposure (ATSDR, 2012; Hartwig, 2012; Health Canada, 2016).

10.2 Bioavailability

10.2.1 Information from solubility studies

The critical aspect to be considered for read-across is whether it can be reasonably assumed that barium chromate reaches the target organs/cells to cause CMR effects. The toxicokinetic data reported by Miyai and colleagues (1980; 1980) indicate that chromium from barium chromate becomes systemically available after inhalation/intratracheal exposure, but to a lower extent than for the more soluble chromates. Urinary excretion data show a bioavailability of ca. 6% after intratracheal injection. Retention times in the lung are higher than for soluble chromates indicating a depot effect after the external exposure has ceased. No further experimental data on bioavailability have been identified beside these Japanese publications, for which only English summaries are available. Therefore, additional information on physico-chemical properties is used to assess the bioavailability of barium chromate after inhalation, oral or dermal exposure.

Information on water solubility of barium chromate is only available from some very old publications with insufficient documentation. These publications indicate that barium chromate is sparsely soluble in water (about 3 – 10 mg/L; see Table 8). Barium chromate is even less soluble in water than other sparingly soluble chromates such as strontium chromate or zinc potassium chromate (see Table 9).

Table 8: Water solubility of barium chromate

g/L	mol/L*	Remark	Reference
0.0026	1.0×10^{-5}		ECHA Dissemination (2021)
0.0033	1.3×10^{-5}		Henderson and Kracek (1927)
0.010	4.0×10^{-5}	At RT; “ordinary” salt – no further information	Beyer and Rieman (1943)
0.006	2.5×10^{-5}	At RT; “ignited” salt – no further information	Beyer and Rieman (1943)
0.008	3.2×10^{-5}	At 25°C	Kohlrausch (1908)
0.004	1.6×10^{-5}		Waddell (1918)
0.0046	1.8×10^{-5}	At 30°C	Miyai et al. (1980)

**Conversion from mg/L to mmol/L and vice versa taking into account the molecular weight of barium chromate of 253.37 g/mol.; **no experimental study available, water solubility based on secondary literature*

Table 9: Water solubility of sparingly soluble chromates

Substance		CAS No.	g/L	Remark	Reference
Strontium chromate	$SrCrO_4$	7789-06-2	1.2	At 20°C	ECHA Dissemination (2021)
Zinc potassium chromate (potassium hydroxy octaoxodizincate dichromate)	$KZn_2(CrO_4)_2(OH)$ and others	11103-86-9	0.5	At 20°C	ECHA Dissemination (2021)
Pentazinc chromate octahydroxide	$Zn_5(OH)_8CrO_4$	49663-84-5	< 0.5	At 20°C	ECHA Dissemination (2021)
Zinc tetrahydroxy chromate (basic zinc chromate: zinc chromate oxide (Zn2(CrO4)O), monohydrate)	$Zn_2CrO_4(OH)_2$ and others	15930-94-6	0.010 – 0.30 0.04		Hartwig and MAK Commission (2012)
Lead chromate	$PbCrO_4$	7758-97-6	0.058	At 20°C	Hartwig and MAK Commission (2012)
Zinc chromate	$ZnCrO_4$	13530-65-9	0.058-0.117		Hartwig and MAK Commission (2012)

From the substances in Table 9 only zinc tetrahydroxy chromate, zinc chromate and lead chromate are of a similar low water solubility as barium chromate. Lead chromate, which also has a comparable low water solubility, was not selected as read-across substance, as it would be difficult to differentiate the contribution of the lead cation to the overall toxicity of the substance. Therefore, data from zinc tetrahydroxy chromate and zinc chromate are discussed and used for the read-across.

Water solubility is not the only criteria to be considered and may not be indicative of solubility in certain body fluids. Solubility in (artificial) body fluids like gastric juice or lung lining fluid should also be considered (see section 1.3.2.1. of ECHA Guidance on the application of the CLP criteria "*Bioavailability of a substance or a mixture is normally assumed if there are in vitro studies available which show the solubility of a substance or mixture in body fluids or artificial simulated body fluids.*"; ECHA (2017)). However, there is no information available on the solubility of barium chromate in (artificial) body fluids, which could be used.

There is some evidence that solubility of barium chromate could be increased under acidic conditions: Waddell (1918) developed a method for the quantification of barium chromate which relies on the solution of barium chromate in diluted hydrochloric acid and subsequent titration with sodium thiosulfate in the presence of potassium iodide. Also, Ahmad et al. (2014) reported an increase in the amount of barium chromate soluble in water with increasing amounts of hydrochloric acid and pH values around 3. Further, experimental data investigating *in vitro* mutagenicity of poorly soluble chromates reported increased effects if the test item is solubilised in an acid solution. For example, basic zinc chromate revealed positive effects in a sister chromatid exchange assay when the substance was dissolved in hydrochloric acid (Levis and Majone, 1981). Addition of nitrilotriacetic acid (NTA) to the test material formulation increased the induction of sister chromatid exchanges by barium chromate, zinc chromate and lead chromate and bacterial reverse mutations by barium chromate and zinc chromate (Venier et al., 1985). Whether the increase in the presence of NTA is due to the acidic conditions or due to a complex-formation of NTA with Ba^{2+} or other cations and resulting increased availability of chromate (CrO_4^{2-}) is a matter of discussion.

The data indicate that an increased solubility of barium chromate under acidic conditions and, hence, an increased solubility in gastric juice after oral application could reasonably be assumed. At the same time it has to be considered that there are effective reductive systems in place in the gastrointestinal tract which can reduce Cr(VI) to Cr(III) before Cr(VI) becomes systemically available or enters the cells of the gastrointestinal

mucous membrane. Experimental data from animals and humans indicate that systemic bioavailability as well as bioavailability of Cr(VI) in the cells of the gastrointestinal mucosa may be increased if the chromium reducing systems in the gastrointestinal tract are exhausted (Health Canada, 2016). Further, carcinogenic effects at the site of entry (i.e. stomach, forestomach, duodenum, jejunum) are described for the soluble potassium and sodium dichromate after oral application (ATSDR, 2012). In the absence of reliable experimental or epidemiologic studies on carcinogenicity of poorly soluble Cr(VI) compounds after oral application it remains speculative whether they could reach sufficiently high extracellular Cr(VI) concentrations to cause local carcinogenic effects in the gastrointestinal tract or whether these compounds are efficiently reduced before they reach the intracellular space. No firm conclusion on the bioavailability of barium chromate after oral exposure can be drawn.

The investigations of Miyai and coworkers (1980; 1980) point to a low bioavailability of barium chromate after inhalation/intrabronchial exposure. A nearly neutral pH value can be assumed for the lung lining fluid: ECETOC (2013) gives a pH of 7.4 for interstitial fluid and artificial alveolar fluid. A pH around 7.4 for the epithelial lining fluid was also reported by Zielinski et al. (1999). Ng et al. (2004) report that the pH of airway surface liquid in humans is about pH 6.6. Therefore, no – or only a marginal - increase of barium chromate solubility in the lung fluids could be assumed due to pH. Considering the slight acid pH of macrophage lysosomes, which is in the range of pH 4 to 5 (DiCiccio and Steinberg, 2011; Li et al., 2019), an accumulation of barium chromate in macrophages and a consequently prolonged availability in the lung but also dissolution might be possible, which would be in accordance with the observation of Miyai and colleagues.

10.2.2 Information from experimental studies

Cohen et al. (1998) exposed Fisher 344 rats for 2-4 weeks to 360 µg Cr/m^3 either as potassium chromate or barium chromate. At the end of the exposure time bronchopulmonary lavage was collected and effects on cells in the lavage fluid (e.g., number of macrophages, neutrophils, monocytes, total cell number, cytokine production of pulmonary macrophages and formation of reactive oxygen intermediates) were analysed. For example, barium chromate exposure increased the percentage of neutrophils and decreased the percentage of macrophages. Similar but more pronounced effects were observed for potassium chromate, while the barium chromate effects did not differ statistically significant from controls. Barium chromate had also less of an effect on the modulation of alveolar macrophage-inducible interleukins-1 and -6 and tumour necrosis factor alpha production than potassium chromate. As all parameters were measured in cells of the lavage fluid and not in epithelial cells, no information on bioavailability of barium chromate in epithelial cells is available from this study.

There are no *in vivo* studies on acute or repeated dose toxicity after exposure to barium chromate. In the absence of such data no comparison of the effect levels and extent of effects elicited by barium chromate and other chromates can be made. Therefore, it remains unclear to which extent barium chromate will become available to target cells after e.g. oral or inhalation exposure.

Evidence for intracellular bioavailability of Cr(VI) after barium chromate exposure comes from *in vitro* investigations. Several *in vitro* studies report mutagenic effects after exposure to barium chromate (see section 11.8). Additionally, Wise and colleagues (2010; 2004) measured intracellular chromium (VI) concentrations in WTHBF-6 cells (clonal cell line derived from primary human bronchial fibroblasts) after 24 h exposure to different concentrations of barium chromate and detected in two independent experiments a dose dependent increase of intracellular chromium ion concentrations (intracellular concentrations of 13, 113, 393, 1103, 1174 and 2396 µM at 0.01, 0.05, 0.1, 0.5, 1 and 5 µg/cm^2, respectively; in 2004 the authors reported intracellular chromium ion concentrations of 664, 1,863, 1,983, and 4,049 µM at 0.1, 0.5, 1, and 5 µg/cm^2). In these experiments a dose dependent increase of chromosome aberrations was observed.

In summary, there are only limited *in vitro* data available to assess the bioavailability of barium chromate. *In vitro* studies with WTHBF-6 cells indicate that chromium becomes intracellularly bioavailable under *in vitro* conditions which also induced clastogenic effects. Based on these observations it can reasonably be assumed that barium chromate is bioavailable in lung cells after inhalation. Additionally, toxicokinetic investigations indicate a low systemic bioavailability after inhalation/intratracheal application.

10.3 Comparison of effects of different chromates

Data on mutagenic and carcinogenic activity of barium chromate, zinc chromate and zinc tetrahydroxy chromate are compared in the following section. Zinc chromate and zinc tetrahydroxy chromate were selected as read-across substances for barium chromate due to their similar solubility in water.

10.3.1 Carcinogenic effects

Information on carcinogenicity of barium chromate after intrabronchial, intrapleural or intramuscular application did not indicate a carcinogenic effect. Only in one study with intrapleural application one animal developed a tumour at the application site (Hueper, 1961), but no tumour was seen in the study of Levy and Martin (1986) with more than threefold-higher number of animals and intrabronchial application or in any other study of Hueper after intrapleural or intramuscular application (see Table 10).

Similar results as for barium chromate were obtained for zinc tetrahydroxy chromate: Only 1/100 rats developed a bronchial carcinoma after intrabronchial pellet implantation (Levy and Martin, 1986). I.e. the experimental data for the two chromates with the lowest solubility (see section 11.9) did not show a clear carcinogenic effect in experimental studies. Zinc chromate induced local tumours in 5 or 3 of hundred rats depending on the type of test material tested (Levy and Martin, 1986). Other poorly soluble chromates – but with a higher water solubility than barium chromate - like strontium chromate induced local tumours in 43 or 23 of hundred rats under identical conditions (Levy and Martin, 1986). These data indicate that small differences in solubility could influence the outcome of the carcinogenic assays and supports the assumption that barium chromate is closer related to zinc chromate and zinc tetrahydroxy chromate than to the other chromates with low solubility. However, all these animal studies are of limited quality and do not allow a conclusive assessment of the carcinogenicity of barium and zinc chromates (see section 11.9).

Table 10: Summary of carcinogenicity data for different chromates

Study details	Result	Reference
Barium chromate		
intrabronchial pellet implantation, 2 years Porton Wistar rats Vehicle: Cholesterol	Number of animals with local tumours: **Test Group:** 0/101 **Negative control:** 1/100 (1 male with phaeochromocytoma)	Levy and Martin (1986)
intrapleural application, 2 years Rats, no information on the sex of the animals Vehicle: Sheep fat	Number of animals with local tumours: **Test group:** 1/31 (latent period. 14 month) **Negative control:** 0/34	Hueper (1961)
intrapleural application, 1 year Bethesda Black Strain rats Vehicle: Sheep fat	Number of animals with local tumours: **Test group:** 0/35 **Negative control:** 0/35	Hueper and Payne (1959)
intramuscular application, 2 years Rats Vehicle: Sheep fat	Number of animals with local tumours: **Test group:** 0/34 (latent period. 14 month) **Negative control:** 0/32	Hueper (1961)
intramuscular application, 1 year Bethesda Black Strain rats Vehicle: Sheep fat	Number of animals with local tumours: **Test group:** 0/35 **Negative control:** 0/35	Hueper and Payne (1959)

Study details	Result	Reference
Zinc tetrahydroxy chromate		
intrabronchial pellet implantation, 2 years Porton Wistar rats Vehicle: Cholesterol	Number of animals with local tumours: **Test Group:** 1/100 **Negative control:** 1/100 (1 male with phaeochromocytoma)	Levy and Martin (1986)
Zinc chromate (low water solubility, no further information)		
intrabronchial pellet implantation, 2 years Porton Wistar rats Vehicle: Cholesterol	Number of animals with local tumours: **Test Group:** 5/100 **Negative control:** 1/100 (1 male with phaeochromocytoma)	Levy and Martin (1986)
Zinc chromate (norge composition, no further information)		
intrabronchial pellet implantation, 2 years Porton Wistar rats Vehicle: Cholesterol	Number of animals with local tumours: **Test Group:** 3/100 **Negative control:** 1/100 (1 male with phaeochromocytoma)	Levy and Martin (1986)
Strontium chromate		
intrabronchial pellet implantation, 2 years Porton Wistar rats Vehicle: Cholesterol	Number of animals with local tumours: **Test Group:** 43/100 or 23/100 (two independent experiments) **Negative control:** 1/100 (1 male with phaeochromocytoma)	Levy and Martin (1986)

10.3.2 Mutagenic effects

A comparison of mutagenic effects for chromates with comparable solubility to barium chromate is compiled in the table below. It has to be noted that no data for zinc tetrahydroxychromate was identified, only for basic zinc chromate which contains zinc tetrahydroxychromate plus 10% chromium trioxide. Effects for barium chromate, basic zinc chromate and zinc chromate are summarised below:

- Induction of chromosome aberrations *in vitro*: comparable potency of barium chromate and zinc chromate for the induction of damaged metaphases (Wise et al., 2010); positive results were also reported for basic zinc chromate when the substance was dissolved in hydrochloric acid (De Flora et al., 1990).
- Sister chromatid exchanges *in vitro*: positive effects are reported for barium chromate, basic zinc chromate and zinc chromate, the effects of all three substances are increased in the presence of NTA (Venier et al., 1985).
- Bacterial reverse mutation assay: barium chromate was positive in a bacterial reverse mutation assay in TA 100 with and without metabolic activation (MA), but only in the presence of nitrilotriacetic acid trisodium salt (NTA); basic zinc chromate was positive in TA100, TA98, TA1537 and TA1538 without NTA (results from different publications and labs; De Flora et al., 1990).

- Induction of double strand breaks *in vitro*: comparable potency of barium chromate and zinc chromate; zinc chromate showed slightly higher potency, but in the same order of magnitude at similar concentrations (Wise et al., 2010).
- Cell transformation: positive results were obtained in Syrian Hamster Embryo (SHE) cells with barium chromate, basic zinc chromate and zinc chromate; barium chromate was the least active substance (Elias et al., 1989)

The observation that all three substances show comparable mutagenic effects (similar endpoints and effects are observed at comparable concentrations) supports the hypothesis that mutagenic effects of barium chromate can be assessed on basis of the findings for zinc chromate and zinc tetrahydroxy chromate.

Table 11: Compilation of *in vitro* genotoxicity data for different chromium compounds

Test type	Barium Chromate	Basic zinc chromate (zinc tetrahydroxy chromate plus 10% chromium trioxide)	Zinc chromate
Chromosome aberration	Positive (at 0.01, 0.05, 0.1, and 0.5 µg/cm^2; cytotoxic at higher concentrations) [a)]	Positive at 5 µg/ml; incidence increased when dissolved in NaOH [b)]	Positive (at 0.01, 0.05, 0.1, and 0.5 µg/cm^2; cytotoxic at higher concentrations) [a)]
Sister chromatid exchange	Positive, effect further increased in the presence of NTA [c)]	Positive at 5 µg/ml; incidence increased when dissolved in NaOH [b)] Positive, effect further increased in the presence of NTA [c)]	Positive, effect further increased in the presence of NTA [c)]
Double strand breaks	Dose dependent increase at concentrations up to 1.0 µg/cm^2 [a)]	No data	Dose dependent increase at concentrations up to 0.5 µg/cm^2 [a)]
Bacterial reverse mutation	Positive in TA 100 in presence of NTA [c)]	Positive in TA100, TA98, TA1537 and TA1538 without NTA, negative in TA 1535 [d)]	Positive in TA 100, effect increased in the presence of NTA [c)]
Cell transformation	Positive in SHE cells, but only weak transformation activity [e)]	Positive in SHE cells [e)]	Positive in SHE cells [f)], BHK-fibroblasts [g))]

a) Wise et al. (2010); b) Levis and Majone (1981); c) Venier et al. (1985); d) De Flora (1981); e) Elias et al. (1989); f) Casto et al. (1979), g) Hansen and Stern (1985),

10.3.3 Effects on reproductive toxicity

No studies investigating reproductive toxicity of barium chromate, zinc chromate or zinc tetrahydroxy chromate could be identified. Therefore, no evaluation of barium chromate properties on basis of read-across data could be performed.

10.3.4 Absence of effects for the zinc cation

Health effects of zinc salts like zinc chloride or zinc sulphate have been extensively investigated and reviewed by several agencies. Altogether, none of these compounds have been identified as producing carcinogenic, mutagenic or reproductive toxic effects (ECHA C&L Inventory, 2021), indicating the effects observed with zinc chromate or zinc tetrahydroxchromate are probably due to the chromate anion and not due to the zinc cation.

10.4 Overall evaluation

The chromate ion is most likely causing the carcinogenic effect of all chromates. The release of the chromate ion depends on its solubility in physiological fluids. This solubility differs between the different chromates and is expected to affect the potency to induce carcinogenicity but not the potential to induce carcinogenicity. A difference in potency in inducing carcinogenicity is not relevant for the classification as this is based on strength of evidence and not on potency. Overall, existing data point to a comparable water solubility of barium chromate and the possible read-across substances zinc chromate and zinc tetrahydroxy chromate. Investigations on possible mutagenic and carcinogenic effects, especially studies which tested all three substances in parallel, indicate that all three substances possess comparable properties and suggest comparable dissolution under physiological circumstances and therefore support the evaluation of barium chromate on basis of the information available for the source substances zinc chromate and zinc tetrahydroxy chromate.

11 EVALUATION OF HEALTH HAZARDS

Acute toxicity

11.1 Acute toxicity - oral route

Evaluation not performed for this substance.

11.2 Acute toxicity - dermal route

Evaluation not performed for this substance.

11.3 Acute toxicity - inhalation route

Evaluation not performed for this substance.

11.4 Skin corrosion/irritation

Evaluation not performed for this substance.

11.5 Serious eye damage/eye irritation

Evaluation not performed for this substance.

11.6 Respiratory sensitisation

Evaluation not performed for this substance.

11.7 Skin sensitisation

Evaluation not performed for this substance.

11.8 Germ cell mutagenicity

Table 12: Summary table of mutagenicity/genotoxicity tests *in vitro* with barium chromate

Method, guideline, deviations if any	Test substance,	Relevant information about the study including rationale for dose selection (as applicable)	Observations	Reference
Chromosome aberration test No guideline followed GLP: No RL 2	Barium chromate Purity: ≥ 98%	WTHBF-6 cells (clonal cell line derived from primary human bronchial fibroblasts) Exposure duration: 24 h without MA Test concentration: 0.01 – 5 µg/cm^2 (cytotoxicity measured up to 10 µg/cm^2) Cytotoxicity: determined by a clonogenic assay (measuring reduction	Positive for the induction of chromosome aberrations without MA **Relative survival** (percent of control): 88, 74, 67, 12, 3, 0.1 and 0% at 0.01, 0.05, 0.1, 0.5, 1, 5 and 10 µg/cm^2, respectively. **Induction of chromosome aberrations:** Concentration dependent increase in percent damaged metaphases (5, 9, 22, 49% of damaged metaphases at 0.01, 0.05, 0.1, and 0.5 µg/cm^2, respectively) and concentration dependent increase of total damaged	Wise et al. (2002; 2004; 2003)*

Method, guideline, deviations if any	Test substance,	Relevant information about the study including rationale for dose selection (as applicable)	Observations	Reference
		in plating efficiency in treatment groups relative to controls) Assessment of chromatid lesions (chromatid deletions and achromatic lesions) and isochromatid lesions (isochromatid deletions and isochromatid achromatic lesions) 3 independent repeats per experiments Evaluation of 100 metaphases per data point Intracellular chromium measurement using ICPMS Vehicle: acetone Positive control: no	chromosomes (5, 10, 28, 65 aberrations per 100 metaphases at 0.01, 0.05, 0.1, and 0.5 µg/cm^2, respectively). At 1 and 5 µg/cm^2 the cell cycle was delayed, and no metaphases have been observed.	
Double strand breaks No guideline followed GLP: No RL 2	Barium chromate Purity: ≥ 98%	WTHBF-6 cells (clonal cell line derived from primary human bronchial fibroblasts) Exposure duration: 24 h without MA Test concentration: 0.01 – 5 µg/cm^2 Assessment of double strand breaks by immunofluorescence for gamma-H2A.X foci formation Intracellular chromium measurement using ICP-OES Vehicle: acetone Positive control: no	Positive for the induction of double strand breaks without MA **Double strand breaks measured by gama-H2A.X foci formation:** dose dependent increase in foci per cell; 0.5 µg/cm^2 barium chromate induced 9.8 foci per cell; effect statistically different from control at 0.1 and 1 µg/cm^2 ($p < 0.05$). **Intracellular chromium ion concentration**: 13, 113, 393, 1103, 1174, 2396 µM at 0.01, 0.05, 0.1, 0.5, 1 and 5 µg/cm^2, respectively (in 2004 the authors reported intracellular chromium ion concentrations of 664, 1,863, 1,983, and 4,049 µM at 0.1, 0.5, 1, and 5 µg/cm^2; determined with ICPMS)	Wise et al. (2010; 2004)*
Sister chromatid exchange assay No guideline followed	Barium chromate Purity: analytical	Chinese hamster fibroblasts cell line (CHO K1) test concentration: 0.1	Positive result for the induction of SCE (significantly increased over control in the presence of barium chromate).	Venier et al. (1985)*

Method, guideline, deviations if any	Test substance,	Relevant information about the study including rationale for dose selection (as applicable)	Observations	Reference
GLP: No RL 3	grade	µg/ml with or without 0.5 µg/ml NTA (two replicates) Exposure duration: 30 h without MA 50 metaphases (70 metaphases for control cultures) counted to determine the number or SCEs/metaphase and per chromosome Vehicle: double distilled water with or without 0.5 µg NTA/ml)	SCE per metaphase: 8.27 ± 0.26 vs 10.36 ± 0.26 in control and treated cells (without NTA) 8.40 ± 0.33 vs 13.26 ± 0.40 in control and treated cells (with NTA) SCE per chromosome: 0.43 ± 0.013 vs 0.54 ± 0.013 in control and treated cells (without NTA) 0.44 ± 0.017 vs 0.69 ± 0.021 in control and treated cells (with NTA) No information on cytotoxicity	
Sister chromatid exchange assay No guideline followed GLP: No RL 3	Barium chromate Purity: ultra-pure grade	Chinese hamster V79 cells Only one concentration tested: 133 µM (two replicates) Exposure duration: 24 h without MA 30 mitotic cells counted to determine the number or SCEs/cell Vehicle: cell culture medium	Positive result for the induction of SCE, 8.1-fold increase above background (4.48 ± 0.21 vs 36.20 ± 0.10 SCE/cell in control and treated cells; average values from two separate experiments); no information on cytotoxicity	Zelikoff et al. (1988)*
Bacterial reverse mutation assay (plate incorporation assay) *S. typhimurium* TA 100 No guideline followed GLP: No RL 3	Barium chromate Purity: analytical grade	Test concentrations: 0, 80, 160, 320, 640 µg barium chromate /plate with and without MA Vehicles: double-distilled water, 0.5N NaOH; 10 mg/ml NTA; 100 mg/ml NTA Triplicate cultures, two independent experiments	Negative in double-distilled water and 0.5 N NaOH, increased mutation frequency in the presence of NTA without metabolic activation; cytotoxicity observed at the two highest Cr(VI) concentrations with the high NTA concentration (100 mg/ml) in cultures without MA	Venier et al. (1985)*
Neoplastic Transformation assay *in vitro* No guideline followed GLP: No	Barium chromate Purity: p.a., no further information	Syrian hamster embryo (SHE) cells 1, 2, 4, 8 µg Cr/ml Determination of cytotoxicity of the	Weak transformation activity; transformation frequency of 0.18 – 0.24% at concentrations of 0.19-0.37 µg Cr/ml (corresponding to 0.93-1.80 µg $BaCrO_4$/ml)	Elias et al. (1989)*

Method, guideline, deviations if any	Test substance,	Relevant information about the study including rationale for dose selection (as applicable)	Observations	Reference
RL 2		treatment by analysis of cloning efficiency Determination of transformation frequency 7-8 days of exposure		
Analysis of deletion mutations and DNA methylation in G12 cells No guideline followed GLP: No RL 3	Barium chromate Purity: not provided	Chinese hamster G12 lung cells (G12 gpt^+ cells) Test concentrations: 0, 0.05, 0.1, 0.15, 0.20 µg/cm^2 24 h exposure Vehicle: complete F12 medium 2-3 independent experiments	Dose-dependent increase of the mutation frequency, with a maximal mutation peak (3.5× background) observed at 0.15 µg/cm^2 (75% survival). Mutation frequency at 0.15 µg/cm^2 was ca. 110 x 10^{-6} (results only presented in a figure). 33% (8/24) deletion mutants were identified in exposed G12 cells. No induction of any DNA methylation changes was observed in G12 cells.	Klein et al. (2002)*

* Study not included in registration dossier

RL = Klimisch reliability score

ICPMS: inductively coupled plasma mass spectrometer; ICP-OES: Inductively coupled plasma optical emission spectrometer; MA: metabolic activation; NaOH: sodium hydroxide; NTA: nitrilotriacetic acid trisodium salt

Table 13: Summary table of mutagenicity/genotoxicity tests *in vitro* with read-across substances

Method, guideline, deviations if any	Test substance,	Relevant information about the study including rationale for dose selection (as applicable)	Observations	Reference
Chromosome aberration test No guideline followed GLP: No RL 2	Zinc chromate (CAS No. 13530-65-9) Purity: ≥ 98%	WTHBF-6 cells Exposure duration: 24 h without MA (for details see Table 12) Test concentration: 0.1 – 0.5 µg/cm^2 Vehicle: acetone Positive control: no	Positive for the induction of chromosome aberrations without MA **Relative survival** (percent of control): 76, 64, 53, 29, 15, and 5% at 0.1, 0.15, 0.2, 0.3, 0.4, and 0.5 µg/cm^2, respectively. **Induction of chromosome aberrations:** Concentration dependent increase in percent damaged metaphases (ca. 18,	Wise et al. (2010)

Method, guideline, deviations if any	Test substance,	Relevant information about the study including rationale for dose selection (as applicable)	Observations	Reference
			22, 28, 34, 45, and 50% of damaged metaphases at 0.1, 0.15, 0.2, 0.3, 0.4, and 0.5 µg/cm^2, respectively; results read from a figure) and concentration dependent increase of total damaged chromosomes (ca. 21, 27, 36, 41, 60, and 71 aberrations per 100 metaphases at 0.1, 0.15, 0.2, 0.3, 0.4, and 0.5 µg/cm^2, respectively; results read from a figure).	
Chromosome aberration test and Sister chromatid exchanges No guideline followed GLP: No RL 3	Zinc yellow (main Cr(VI) component: basic zinc chromate; chemical composition: zinc tetrahydroxychromate plus 10% chromium trioxide) Purity: no data	Chinese hamster ovary (CHO) cells Exposure duration: 2 division cycles Test concentration: 5 - 150 µg/mL Test concentration in culture medium with NaOH: 0.1 and 0.3 µg/ml Vehicle: Cell culture medium (MEM) or MEM with NaOH No further methodological details Chromosome aberrations and SCE were scored in the same 2nd division metaphases	Positive for the induction of chromosome aberrations and SCE without MA **Substance dissolved in culture medium:** **Cytotoxicity:** Cell growth (% of control): 100, 73, 29, 10% at 0, 5, 25, 150 µg/mL, respectively **Chromosome and chromatid aberrations per 100 metaphases**: 28.6 at 5 µg/mL (14 metaphases counted) vs. 13.3 (61 metaphases counted) in the control group **SCE/metaphase:** 13.14 ± 1.10 at 5 µg/mL (14 metaphases counted) vs. 7.47 ± 0.11 (61 metaphases counted) in the control group **Substance dissolved in culture medium with NaOH (0.005-0.015 N):** **Chromosome and chromatid aberrations per 100 metaphases**: 12.5 and 19.9 at 0.1 and 0.3 µg/mL (40 or 30 metaphases counted, respectively) vs. 10.0 (50 metaphases counted) in the control group **SCE/metaphase:** 9.25 ± 0.28 and 9.17 ± 0.36 at 0.1 and 0.3 µg/mL (40 or 30 metaphases counted, respectively) vs. 7.54 ± 0.16 (50 metaphases counted) in the control group	Levis and Majone (1981)
Sister chromatid exchange assay No guideline	Zinc chromate Purity: analytical grade	Chinese hamster fibroblasts cell line (CHO K1) test concentrations: 0.1 and 0.15 µg/ml with or	Positive result for the induction of SCE (significantly increased over control in the presence of zinc chromate). 0.1 µg/ml zinc chromate and 0.5	Venier et al. (1985)

Method, guideline, deviations if any	Test substance,	Relevant information about the study including rationale for dose selection (as applicable)	Observations	Reference
followed GLP: No RL 3		without 0.5 or 0.05 µg/ml NTA (two replicates) Exposure duration: 30 h without MA (for details see Table 12) Vehicle: double distilled water with or without 0.05 or 0.5 µg NTA/ml)	µg/ml NTA: SCE per metaphase: 7.72 ± 0.22 vs. 9.35 ± 0.18 in control and treated cells (without NTA) 8.03 ± 0.21 vs 11.12 ± 0.36 in control and treated cells (with NTA) SCE per chromosome: 0.40 ± 0.011 vs 0.48 ± 0.009 in control and treated cells (without NTA) 0.41 ± 0.010 vs 0.57 ± 0.018 in control and treated cells (with NTA) 0.15 µg/ml zinc chromate and 0.05 µg/ml NTA: SCE per metaphase: 7.72 ± 0.22 vs. 9.88 ± 0.26 in control and treated cells (without NTA) 8.01 ± 0.22 vs 12.42 ± 0.36 in control and treated cells (with NTA) SCE per chromosome: 0.40 ± 0.011 vs 0.51 ± 0.013 in control and treated cells (without NTA) 0.41 ± 0.011 vs 0.64 ± 0.018 in control and treated cells (with NTA) No information on cytotoxicity	
Sister chromatid exchange assay No guideline followed GLP: No RL 3	Zinc Yellow (90% basic zinc chromate ($ZnCrO_4 \cdot Zn(OH)_2$) Purity: analytical grade	Chinese hamster fibroblasts cell line (CHO K1) test concentration: 0.1 µg/ml with or without 1 µg/ml NTA (two replicates) Exposure duration: 30 h without MA (for details see Table 12) Vehicle: double distilled water with or without 1 µg NTA/ml)	Positive result for the induction of SCE (significantly increased over control in the presence of zinc yellow). SCE per metaphase: 7.70 ± 0.32 vs 8.76 ± 0.27 in control and treated cells (without NTA) 7.74 ± 0.24 vs 10.84 ± 0.38 in control and treated cells (with NTA) SCE per chromosome: 0.40 ± 0.01 vs 0.45 ± 0.01 in control and treated cells (without NTA) 0.40 ± 0.01 vs 0.56 ± 0.01 in control and treated cells (with NTA) No information on cytotoxicity	Venier et al. (1985)
Double strand	Zinc chromate (CAS	WTHBF-6 cells (clonal cell line derived from	Positive for the induction of double	Wise et al.

Method, guideline, deviations if any	Test substance,	Relevant information about the study including rationale for dose selection (as applicable)	Observations	Reference
breaks No guideline followed GLP: No RL 2	No. 13530-65-9) Purity: ≥ 98%	primary human bronchial fibroblasts) Exposure duration: 24 h without MA Test concentration: 0.1-0.5µg/m^3 Assessment of double strand breaks by immunofluorescence for gamma-H2A.X foci formation Intracellular chromium measurement using ICP-OES Vehicle: acetone Positive control: no	strand breaks without MA **Double strand breaks measured by gama-H2A.X foci formation:** dose dependent increase in foci per cell; 0.5 µg/cm^2 zinc chromate induced 13.4 foci per cell; effect statistically different from control at 0.2, 0.3 and 0.4 µg/cm^2 ($p < 0.05$) (results only presented in figure, only the values reported here were presented in the text). **Intracellular chromium ion concentration**: 179, 266, 394, 650, 870, and 1102 µM at 0.1, 0.15, 0.2, 0.3, 0.4, and 0.5 µg/cm^2, respectively	(2010)
Bacterial reverse mutation assay (plate incorporation assay) *S. typhimurium* TA 100 No guideline followed GLP: No RL 3	Zinc chromate Purity: analytical grade	Test concentrations: 0, 20, 40, 80, 160 µg barium chromate /plate with and without MA Vehicles: double-distilled water, 0.5N NaOH; 10 mg/ml NTA; 100 mg/ml NTA Triplicate cultures, two independent experiments	Positive in double-distilled water without MA, no effect of addition of NaOH except increased number of revertants at highest concentration with MA; mutagenicity of zinc chromate slightly increased in the presence of NTA with and without MA (also increased cytotoxicity at the two highest concentrations)	Venier et al. (1985)
Bacterial reverse mutation assay *S. typhimurium* TA 98, TA 100, TA 1535, TA 1537, TA 1538 No information on guideline GLP: no data RL 4	Basic zinc chromate (Zinc Yellow; $ZnCrO_4 \cdot Zn(OH)_2$ + 10% CrO_3) Purity: no data	Several *Salmonella typhimurium* strains Test concentrations: 90-590 nmoles/plate With and without metabolic activation (rat liver S-9 mix) Vehicle: double distilled water or DMSO At least duplicate cultures	Negative in TA 1535 Positive in TA 100 Weak positive (increase of revertants 2 to 3 times the controls) in TA98, 1537 and 1538 Effect in the presence of metabolic activation decreased	De Flora (1981)
Transformation assay (enhancement	Zinc chromate Purity: no data	Primary Syrian hamster embryo (SHE)	Dose dependent enhancement of viral transformation	Casto et al. (1979)

Method, guideline, deviations if any	Test substance,	Relevant information about the study including rationale for dose selection (as applicable)	Observations	Reference
of morphological transformation by the simian adenovirus SA7) No guideline followed GLP: No RL 3		cells Simian adenovirus SA7 cultured in monkey kidney cells Test concentrations: 0, 0.0025, 0.005, 0.01, 0.02 mM Treatment of HEC cells: 18 h prior to virus inoculation or 48 h after inoculation Vehicle: acetone:water (1:1)	Number of foci from 10^6 plated cells: 37, 63, 68, 110, 85 at0, 0.0025, 0.005, 0.01, 0.02 mM, respectively Surviving fraction: 1.00, 0.90, 1.13, 0.73, 0.33 at 0, 0.0025, 0.005, 0.01, 0.02 mM, respectively	
Anchorage independent growth No guideline followed GLP: No RL 3	Zinc chromate Purity: no data	Syrian hamster (BHK) fibroblasts Test concentrations: 5, 10, 20 µg/mL (corresponding to 1.6, 3.1, 6.8 µg Cr(VI)/mL) Treatment duration: 7 h Vehicle: distilled water	Dose dependent decrease of survival, and dose dependent increase of absolute transformation frequency and specific transformation frequency per survivor (ca. 2, 20 and 100 per 5 x 10^5 living cells at 5, 10, 20 µg/mL, respectively – data read from figure)	Hansen and Stern (1985)
Neoplastic Transformation assay *in vitro* No guideline followed GLP: No RL 2	Basic zinc chromate Purity: two structurally different compounds were tested (Zh: $ZnCrO_4 \cdot 3.5\ Zn(OH)_2$, H_2O and Zm: $ZnCrO_4 \cdot 2.5\ Zn(OH)_2$, H_2O	Syrian hamster embryo (SHE) cells 0.05, 0.08, 0.1, 0.2, 0.3, 0.4, 0.6 µg Cr/ml Determination of cytotoxicity of the treatment by analysis of cloning efficiency Determination of transformation frequency 7-8 days of exposure	Induction of transformations Zh compound: transformation frequency of 3.1-3.2 at LD50 (ca. 0.25 µg/ml; results read from a figure) Zm compound: ca. 1.6-fold less potent	Elias et al. (1989)

RL = Klimisch reliability score

11.8.1 Short summary and overall relevance of the provided information on germ cell mutagenicity

Barium chromate has been investigated in several *in vitro* studies for mutagenicity, however no guideline studies or studies according to GLP have been performed. Due to methodological shortcomings or insufficient reporting most of the studies are not reliable. Reliable results were obtained in an *in vitro* assay investigating the induction of chromosome aberrations in a human cell line. Barium chromate induced a dose dependent increase of chromosome aberrations in the absence of metabolic activation (no investigations with metabolic

activation performed), covering a concentration range up to cytotoxic concentrations. In parallel, the chromium concentration in the cells was measured, showing that chromium was taken up by the cells and that the intracellular chromium concentration increased dose dependently. Also, the induction of double strand breaks was demonstrated in this study.

Two other studies investigated the induction of sister chromatid exchanges (SCE), however only single concentrations were tested. These studies report an increase of SCE in the presence of barium chromate, an effect which was even more pronounced in the presence of NTA. The increase of SCE in the presence of NTA might be due to the increased acidity of the test material formulation or due to the complex formation of NTA with the barium ion and a subsequent increase availability of chromate ions.

In a bacterial reverse mutation assay in *Salmonella typhimurium* strain TA 100 a mutagenic effect of barium chromate was only detectable in incubations without metabolic activation and in the presence of NTA. No effect was observed if the test item was applied in water or in a sodium hydroxide solution or in the presence of metabolic activation which is in line with the assumption that metabolic activation systems reduce chromium VI to chromium III.

Positive results were also reported in a neoplastic transformation assay in SHE cells. However, barium chromate revealed only a very low potency in comparison to other chromates, like e.g. zinc chromate, which was tested in parallel. Further, the induction of deletion mutations but no DNA methylation was reported in Chinese hamster G12 lung cells. Altogether, the available *in vitro* tests consistently indicate that barium chromate is mutagenic *in vitro*. However, no tests investigating mutagenicity *in vivo* or toxicokinetic studies documenting that barium chromate reaches the germ cells are available.

Comparable effects are observed for the read-across substances zinc chromate and zinc tetrahydroxy chromate, some of which were even tested under identical experimental conditions (see Table 13 and Table 11). Like for barium chromate the induction of chromosome aberrations, double strand breaks, sister chromatid exchanges, bacterial reverse mutations and cell transformations were reported, indicating that the observed effects are due to the chromate anion of the molecules. Potencies of the different substances were very similar. For example, the clastogenic effects of zinc chromate and barium chromate described by Wise et al. (2010) were similar relative to the tested concentrations. Considering the intracellular Cr-concentration zinc chromate was slightly more potent than barium chromate (less than 1.5-fold higher potency). Similar potencies of zinc and barium chromate were observed for the induction of double strand breaks (Wise et al., 2010). Also the investigations of Venier et al. (1985) revealed very similar potencies of zinc tetrahydroxy chromate, zinc chromate and barium chromate for the induction of SCE (slightly increasing effect in relation to the tested concentration in this order). In the bacterial reverse mutation assay zinc chromate was slightly more potent than barium chromate (Venier et al., 1985). As for barium chromate there are no *in vivo* mutagenicity tests available. Further, there are no toxicokinetic data for the read-across substances, which would allow to assess the possible availability and activity of the read-across substances in germ cells. There is no harmonised classification for the read-across substances for the endpoint germ cell mutagenicity.

Due to this lack of data no assessment of possible germ cell mutagenicity of barium chromate is possible.

Some very soluble chromates such as the sodium, potassium and ammonium form have a harmonised classification as Muta. 1B showing the potential of chromate anions to induce germ cell mutagenicity. However, due to the large differences in water solubility compared to barium chromate a difference in bioavailability is expected and read-across from the very soluble chromates is not considered justified.

11.8.2 Comparison with the CLP criteria

For potential classification on germ cell mutagenicity, criteria from the CLP Regulation (EC, 2008)[1] were applied:

Comparison with Category 1 criteria

[1] REGULATION (EC) No 1272/2008 considering all ATPs published until June 2021

- *The classification in Category 1A is based on positive evidence from human epidemiological studies (EC, 2008)*

There are no epidemiological data to support classification of barium chromate or possible read-across substances in Category 1A.

- *The classification in Category 1B is based on positive result(s) from in vivo heritable germ cell mutagenicity tests in mammals (EC, 2008)*

No *in vivo* studies with heritable germ cell are available.

- *Classification in Category 1B can also be based on "positive result(s) from in vivo somatic cell mutagenicity tests in mammals, in combination with some evidence that the substance has potential to cause mutations to germ cells. It is possible to derive this supporting evidence from mutagenicity/genotoxicity tests in germ cells in vivo, or by demonstrating the ability of the substance or its metabolite(s) to interact with the genetic material of germ cells". (EC, 2008)*

No *in vivo* somatic cell mutagenicity tests in mammals are available for barium chromate and the read-across substances. Further, no data showing that the substance has the potential to cause mutations in germ cells is available. Thus, classification in Category 1B is not supported.

Comparison with Category 2 criteria

- *Classification in category 2 is based on:*

  — positive evidence obtained from experiments in mammals and/or in some cases from in vitro experiments, obtained from:

  — somatic cell mutagenicity tests in vivo, in mammals; or

  — other in vivo somatic cell genotoxicity tests which are supported by positive results from in vitro mutagenicity assays. (EC, 2008)

These criteria are not met as there are no *in vivo* somatic cell genotoxicity tests in mammals with barium chromate or the read-across substances.

Therefore, no classification for germ cell mutagenicity is proposed for barium chromate.

11.8.3 Conclusion on classification and labelling for germ cell mutagenicity

In the absence of relevant studies for germ cell mutagenicity of barium chromate or possible read-across substances no classification for germ cell mutagenicity is proposed for barium chromate.

11.9 Carcinogenicity

Table 14: Summary table of animal studies on carcinogenicity with barium chromate

Method, guideline, deviations if any, species, strain, sex, no/group	**Test substance, dose levels duration of exposure**	**Results**	**Reference**
Carcinogenicity study with intrabronchial pellet implantation No guideline	Barium chromate Purity: 98% Duration: 2 years Implantation of a metal wire basket	**Test Group:** Number of lungs with chronic inflammation: 13 (9 m and 4 f) Number of lungs with bronchial inflammation: 87 (no information on sex of animals)	Levy and Martin (1986)*

Method, guideline, deviations if any, species, strain, sex, no/group	Test substance, dose levels duration of exposure	Results	Reference
followed GLP: No Porton Wistar rats (50 animals per sex per dose group; n=101 animals) RL 3	or pellet containing the test material into the left bronchus; lungs and other organs presenting abnormalities at necropsy were examined microscopically Dose: no data, only one dose tested 10 g test material were mixed with 10 g cholesterol and heated to 160°C; pre-weighed pellet was dipped in the molten mixture Testing of 20 different chromates in parallel. Vehicle: Cholesterol Positive control: 20-methylcholanthrene and calcium chromate	Number of animals with squamous metaplasia: 12 (6 m and 6 f) Number of animals with dysplasia: 2 (0 m and 2 f) Number of animals with bronchial tumours: **0/101** **Negative control:** Number of lungs with chronic inflammation: 7 (4 m and 3 f) Number of lungs with bronchial inflammation: 89 (no information on sex of animals) Number of animals with squamous metaplasia: 7 (3 m and 4 f) Number of animals with dysplasia: 0 Number of animals with tumours: 1/100 (1 m with phaeochromocytoma) **Positive control:** 20-methylcholanthrene and calcium chromate, induction of bronchial carcinomas in 22/48 and 25/100 rats, respectively Survival on day 400: 95.7% (covering all substances) Survival on day 700: 53.9% (covering all substances)	
Carcinogenicity study with intrapleural application No guideline followed GLP: No Rats, total of 31 (treated) or 34 (control) animals, no information on the sex of the animals RL 3	Barium chromate Purity: no data No details of test provided, probably only one dose tested; observation period ca. 2 years Vehicle/negative control: Sheep fat	Local tumours at site of implantation: **Test group:** 1/31 (latent period. 14 month) **Negative control:** 0/34 Survival of test group comparable to control group: 30 animals survived till end of month 12 and five animals till end of month 24	Hueper (1961)*
Carcinogenicity study with intramuscular	Barium chromate Purity: no data	Local tumours at site of implantation: **Test group:** 0/34	Hueper (1961)*

Method, guideline, deviations if any, species, strain, sex, no/group	Test substance, dose levels duration of exposure	Results	Reference
application No guideline followed GLP: No Rats, total of 34 (treated) or 32 (control) animals, no information on the sex of the animals RL 3	No details of test provided, probably only one dose tested; observation period ca. 2 years Vehicle/negative control: Sheep fat	**Negative control:** 0/32 Survival of test group comparable to control group: 30 animals survived till end of month 12 and six (control group) or seven animals (treatment group) till end of month 24	
Carcinogenicity study with intrapleural application No guideline followed GLP: No Bethesda Black Strain rats, 35 animals (20 m and 15 f per group) RL 3	Barium chromate Purity: no data No details of test provided, only one dose tested (pellet made of 25 mg chromium compound and 50 g sheep fat) Vehicle/negative control: Sheep fat Observation period: 12 months	Local tumours at site of implantation: **Test group:** 0/35 **Negative control:** 0/35 Survival of test group comparable to control group: 30 animals survived till end of month 12 in both groups	Hueper and Payne (1959)*
Carcinogenicity study with intramuscular application No guideline followed GLP: No Bethesda Black Strain rats, 35 animals (20 m and 15 f per group) RL 3	Barium chromate Purity: no data No details of test provided, only one dose tested (pellet made of 25 mg chromium compound and 50 g sheep fat) Vehicle/negative control: Sheep fat Observation period: 12 months	Local tumours at site of implantation: **Test group:** 0/35 **Negative control:** 0/35 Survival of test group comparable to control group: 30 and 29 animals survived till end of month in the treatment and control group, respectively	Hueper and Payne (1959)*

Method, guideline, deviations if any, species, strain, sex, no/group	Test substance, dose levels duration of exposure	Results	Reference

RL = Klimisch reliability score

* Study not included in registration dossier

Table 15: Summary table of animal studies on carcinogenicity with read-across substances

Type of data/report	Relevant information about the study (as applicable)	Observations	Reference
Carcinogenicity study with intrabronchial pellet implantation No guideline followed GLP: No Porton Wistar rats (50 animals per sex per dose group; n=101 animals) RL 3	Zinc chromate (low solubility) Purity: not stated (39.4% ZnO; 40.8% CrO_3) Duration: 2 years For methodological details see Table 14	**Test Group:** Number of lungs with chronic inflammation: 8 (4 m and 4 f) Number of lungs with bronchial inflammation: 76 (no information on sex of animals) Number of animals with squamous metaplasia: 13 (7 m and 6 f) Number of animals with dysplasia: 2 (2 m and 0 f) Number of animals with tumours: 5/100 (3 m and 2 f; SCC, squamous cell carcinoma) **Negative control:** See Table 14 **Positive control:** See Table 14	Levy and Martin (1986)
Carcinogenicity study with intrabronchial pellet implantation No guideline followed GLP: No Porton Wistar rats (50 animals per sex per dose group; n=101 animals) RL 3	Zinc chromate (“Norge”) Purity: not stated (39.2% ZnO; 43.5% CrO_3) Duration: 2 years For methodological details see Table 14	**Test Group:** Number of lungs with chronic inflammation: 4 (4 m and 0 f) Number of lungs with bronchial inflammation: 86 (no information on sex of animals) Number of animals with squamous metaplasia: 4 (2 m and 2 f) Number of animals with dysplasia: 0 (0 m and 0 f) Number of animals with tumours: 3/100 **(**2 m and 1 f; SCC, squamous cell carcinoma) **Negative control:** See Table 14 **Positive control:** See Table 14	Levy and Martin (1986)

Type of data/report	Relevant information about the study (as applicable)	Observations	Reference
Carcinogenicity study with intrabronchial pellet implantation No guideline followed GLP: No Porton Wistar rats (50 animals per sex per dose group; n=101 animals) RL 3	Zinc tetrahydroxychromate Purity not stated (56.6% Zn; 8.8% Cr) Duration: 2 years For methodological details see Table 14	**Test Group:** Number of lungs with chronic inflammation: 15 (12 m and 3 f) Number of lungs with bronchial inflammation: 82 (no information on sex of animals) Number of animals with squamous metaplasia: 6 (3 m and 3 f) Number of animals with dysplasia: 1 (1 m and 2 f) Number of animals with tumours: 1/100 **(**1 m and 0 f; SCC, squamous cell carcinoma) **Negative control:** See Table 14 **Positive control:** See Table 14	Levy and Martin (1986)
Carcinogenicity study with intrapleural application No guideline followed GLP: No Rats, total of 33 (treated) or 34 (control) animals, no information on the sex of the animals RL 3	Zinc Yellow (no further information)* Purity: no data No details of test provided, probably only one dose tested; observation period ca. 2 years Vehicle/negative control: Sheep fat	Local tumours at site of implantation: **Test group:** 22/33 (latent period. min. 6 month, mean14 month) **Negative control:** 0/34 Survival of test group comparable to control group: 30 animals survived till end of month 12 and five animals till end of month 24	Hueper (1961)
Carcinogenicity study with intramuscular application No guideline followed GLP: No Rats, total of 34 (treated) or 32 (control) animals, no information on the sex of the animals RL 3	Zinc Yellow (no further information)* Purity: no data No details of test provided, probably only one dose tested Vehicle/negative control: Sheep fat	Local tumours at site of implantation: **Test group:** 16/34 (latent period. min. 5 month, mean 6 month) **Negative control:** 0/32 Survival of test group comparable to control group: 30 animals survived till end of month 12 and six (control group) or seven animals (treatment group) till end of month 24	Hueper (1961)

Type of data/report	Relevant information about the study (as applicable)	Observations	Reference

*according to IARC (1990) "zinc yellow" can refer to several zinc chromate pigments, for example basic zinc chromate (= zinc tetrahydroxychromate) or zinc potassium chromate

Table 16: Summary table of human data on carcinogenicity with read-across substances

Type of data/report	Exposure	Relevant information about the study (as applicable)	Observations	Reference
Cohort study covering one Norwegian plant RL 3	Zinc chromate and lead chromate pigments Chromate pigment production period: 1948-1972 Exposure to zinc chromate started in 1951. A small number of workers had also been exposed to lead chromate between 1948 and 1956. No exposure measurement available for the years before 1973. Exposure measurements in 1973: 0.01-1.35 mg Cr/m^3.	Norwegian company producing chromate pigments Total number of male workers: 133 24 workers have been employed for more than 3 years 18 workers have been employed for more than 5 years Observation period: 1953-1980 Reference population: national Norwegian cancer incidence rates among males 1955-1976	One case of lung cancer occurred among 109 workers with less than three years of employment prior to 1972. Six cases of lung cancer occurred in a subpopulation of 24 workers with more than three years of work experience prior to 1972 (observed/expected ratio: 44)). Five of the cases had only worked in the production of zinc chromate; one of the cases had worked in the production of zinc chromate and lead chromate. Five of six patients smoked. Additionally, cancer of the nasal cavity, of the prostate and the gastrointestinal tract were observed.	Langard and Vigander, (1983)
Cohort study covering 3 UK plants RL 3	**Factory A and B:** Production of zinc chromate and lead chromate **Factory C:** Production of lead chromate To produce	**Factory A:** production from 1920 until 1982; production of small amounts of barium chromate from 1942 **Factory B:** production since 1920s until 1978; from early 1950s until about 1968 small amounts of strontium chromate were	Lung cancer incidences were increased in workers with high and medium exposure entering factory A before 1955 and factory B before 1968; therefore, further analysis focused on 298 men with high and medium exposure joining A during 1932 – 54 and B during 1948-67: A: 21 observed/9.45 expected; RR 2.22 B: 11 observed/2.5 expected; RR 4.44 No increased incidences were observed in	Davies (1984)

Type of data/report	Exposure	Relevant information about the study (as applicable)	Observations	Reference
	zinc chromate, zinc oxide powder was reacted with chromic acid or sodium dichromate; precipitates were washed, filtered, stove dried, ground, blended and packed Lead chromate was produced by reaction of metallic lead, lead nitrate or lead acetate with sodium chromate or dichromate	produced (ca. 20 tons in all) **Factory C:** production from 1929; still active at time of update Observation period: from 1930s or 1940s until 1981; analysis in relation to date and duration and severity of exposure Study covers all male workers (except office staff) completing at least one year's service by 30 June 1975 Total number of male workers: 1152 Exposure level: assessed only qualitatively (high, medium, low); as workers changed jobs no clear exposure assignment to different chromates could be made. High exposure resulted mainly from activities with the pigments (drying, grinding, blending and packing). Reference population: mortality England and Wales	any exposure group in factory C, which only produced lead chromate C: 7 observed/6.45 expected; RR 1.1	
Cohort study, prospective RL3	Zinc chromate and lead chromate pigments	France, Lead and zinc chromate pigments Total number of male workers: 251 Inclusion criteria: at least 6 months of employment during the observation period Observation period: 1958-1977 Reference population: standard death rates, northern France 1958-1977	Total number of deaths: 50, specific cause of death available from medical records only for 30 workers Relative risk lung cancer: 4.61 (11 deaths; 95% CI, 2.7-7.9); expected: 2.38 cases Mean time from first employment until detection of cancer: 17 years Mean duration of employment among cases: 15.3 years	Haguenoer et al. (1981)
Historical prospective cohort study, covering 5 factories (3 in Germany, two in The Netherlands) RL3	Zinc chromate and lead chromate pigments Exposure assessment (only qualitative): High exposure: assigned to	Germany and The Netherlands, lead and zinc chromate pigments Male workers employed for at least 6 months by the year 1976. "Relevant" cohort: - Minimum observation period of 10 years since employment started;	Overall mortality was not increased in pigment workers. Number of observed lung cancer deaths were higher than expected in all factories, this effect was statistically significant only in one factory. In only one factory (factory 5) there was a case of death from lung cancer observed in the "low exposure" category compared with 0.9 expected; in no other factory was lung cancer observed in the low exposure	Frentzel-Beyme (1983)

Type of data/report	Exposure	Relevant information about the study (as applicable)	Observations	Reference
	drying and milling of the filtered pigment paste. Medium exposure: assigned to wet processes like precipitation of the pigment, filtering, maintenance, craftsmen, cleaning. Low exposure: assigned to storage, despatch activities, laboratory personnel and supervisors. Influence of smoking habits and other exposures not assessed.	consequently, beginning of exposure period latest 1965. - Complete records for the entire staff. - Exclusion of foreign nationals Study group: 1912 workers (496, 380, 166, 179, 691 in factory 1, 2, 3, 4, 5, respectively), but only 978 workers (319, 141, 97, 174, 247 in factory 1, 2, 3, 4, 5, respectively) in “relevant” cohort Reference population: local death rates, Germany and The Netherlands	group. In the "high exposure" category there were consistently more deaths from lung cancer than would have been expected if the workers, as part of the total population, were subjected to a "normal" risk. A small to marked increase in the number of lung cancer deaths is also found in the medium category. Other tumour locations, such as stomach cancer, prostate cancer, cancer of the intestines or liver cancer, were observed rarely or not at all.	
Cohort study covering one plant in New Jersey (USA) RL3	Zinc chromate and lead chromate pigments Ratio lead chromate:zinc chromate about 9:1 (low levels of nickel may have been present) Exposure only measured during later years, resulting in estimates of >0.5 mg/m^3 for exposed jobs and of >2	USA, lead and zinc chromate pigments Total number of male workers: 1879 Workers had been employed for at least one month between January 1940 and December 1969 Observation period: 1940-1982 Reference population: mortality, US whites and non-whites	No significant excess was observed for lung cancer or cancer at other sites for the entire study group. SMR all cancers: 93 (101 deaths; 95% CI, 76-113). SMR lung cancer death all workers: 116 (41 deaths; 95% CI, 83-158); 24 of these lung cancer deaths among workers exposed to chromate dust (SMR 143). SMR lung cancer death among workers not exposed to chromium: 92 (17 deaths; 95% CI, 53-147). SMR lung cancer death among workers with cumulative exposure to chromate dusts of one to nine years: 176 (9 deaths; 95% CI, 80-334). SMR lung cancer death among workers with cumulative exposure to chromate dusts for ten or more years: 194 (8 deaths; 95% CI, 83-383).	Hayes et al. (1989)

Type of data/report	Exposure	Relevant information about the study (as applicable)	Observations	Reference
	mg/m^3 for highly exposed jobs		SMR lung cancer death among workers with cumulative exposure to chromate dusts for 30 years since employment: 321 (6 deaths; 95% CI, 117-698).	

SMR: standardized mortality ratio

11.9.1 Short summary and overall relevance of the provided information on carcinogenicity

There are no epidemiological studies investigating carcinogenicity of barium chromate. Only the study of Davies et al. reports that workers of factory A were exposed to small amounts of barium chromate. However, as barium chromate exposure was low in relation to the exposure to the other chromate pigments no correlations between barium chromate exposure and effects were possible. There are no cancer studies in experimental animals according to testing guidelines with barium chromate. The potential carcinogenicity of barium chromate was investigated in rats in 5 experimental studies with intrabronchial (1x), intrapleural (2x) or intramuscular (2x) application. None of these studies is from a today's perspective reliable. The non-physiological route of exposure, the use of single implantations and the use of a single dose per substance make the results questionable especially in case of a negative result. The number of animals is in some cases too low and information on the sex of the animals is missing. Further, information on the purity of the substance is not always given, information beyond the reporting of the cancer incidences is missing in most cases (*e.g.* no information on overall appearance, body weight, survival, etc.). Despite these shortcomings the outcome of the studies is highly consistent: barium chromate did not induce tumours in any of these studies, except in one study with intrapleural application, where a local tumour was observed at the site of implantation after intrapleural application.

However, this observation does not unequivocally rule out that barium chromate could induce cancer. Similar observations in animal experiments have been made with zinc tetrahydroxychromate which induced squamous cell carcinoma of the lung in 1/100 rats after intrabronchial application (Levy and Martin, 1986). Two different modifications of zinc chromate, which were also investigated in this study, induced squamous cell carcinoma in 3/100 or 5/100 rats, i.e. only a very low incidence. The low tumour incidence especially for zinc chromate, which is classified as category 1A carcinogen, reveals the limitations of this type of animal experiments.

Epidemiological studies on zinc chromate report an increased incidence of lung tumours for workers exposed to high concentrations of zinc chromate in the form of chromate pigments whereas no such clear causal relation could be demonstrated for lead chromate (Davies, 1984). Apart from all limitations of the epidemiological data (especially inadequate quantitative exposure data, mixed exposure to other chromates, insufficient characterisation of study population, insufficient consideration of influencing factors like smoking) a clear correlation between zinc chromate exposure and induction of lung tumours in humans could be demonstrated which resulted in an evaluation by IARC as "*sufficient evidence in humans for the carcinogenicity of chromium [VI] compounds as encountered in … chromate pigment production.…"* Based on the studies in experimental animals with zinc chromate described above IARC further concluded, that "*There is sufficient evidence in experimental animals for the carcinogenicity of … zinc chromates… "* In addition, zinc chromates are classified as carcinogen category 1A (CLP Annex VI, entry 024-007-00-3).

As outlined in section 10 read-across considerations support the similarities between barium chromate and the sparsely soluble chromates zinc chromate and zinc tetrahydroxy chromate. Additionally, barium chromate triggers effects which are involved in the induction of lung tumours by chromates (reviewed for example by Hartwig and MAK Commission, 2012; Proctor et al., 2014; Urbano et al., 2012). According to these reviews induction of chromium VI related lung tumours is the result of a sequence of different steps which can be summarised in a simplified way as follows:

1) Particulate chromium deposits and accumulates in the bifurcations of the lung. If this results in an exceedance of clearance mechanisms cellular absorption of chromium VI results.
2) Intracellular reduction of chromium VI induces oxidative stress and the formation of chromium III which can interact with the DNA and proteins.

3) The resulting protein and DNA damage may lead to tissue irritation, inflammation, and cytotoxicity.
4) These effects together with increased cell proliferation can result in changes to DNA sequences and finally lead to tumorigenesis.

Although there are only limited experimental studies with barium chromate available and not all key events for the induction of lung tumours have been investigated in the presence of barium chromate, barium chromate data show that

- Barium chromate is absorbed into the cells despite its limited solubility.
- Barium chromate induces mutagenic effects comparable to the effects observed with other (carcinogenic) chromates (see section 10). Barium chromate induces neoplastic transformations *in vitro*, however with lower potency than other chromates.
- Beaver et al. (2009a; 2009b) reported the induction of lung inflammation, injury and proliferation after exposure of mice to the sparsely soluble basic zinc chromate. Already single exposure induced a neutrophilic inflammatory airway response characterised inter alia by an increased number of neutrophils and a decrease of macrophages in lung airways as analysed in broncho alveolar fluid. In a similar manner Cohen et al. (1998) observed an increase in the number of neutrophils and a decrease in the number of alveolar macrophages in the bronchoalveolar lavage of rats treated for 2 or 4 weeks with barium chromate, indicating that both substances induce similar effects.
- Levy and Martin (1986) reported an increased number of lungs with chronic inflammation and with bronchial inflammation with similar extend for barium chromate, zinc chromate and zinc tetrahydroxy chromate.

These data indicate that barium chromate can induce effects associated with the induction of lung tumours typically observed for chromium VI. Therefore, an induction of lung tumours after inhalation exposure to sufficient high barium chromate amounts seems to be plausible despite some uncertainty to the bioavailability of the chromate anion due to the low solubility of the substance.

No information is available on the induction of tumours after oral application, neither for barium chromate nor for the read-across substances.

11.9.2 Comparison with the CLP criteria

For potential classification on carcinogenicity, criteria from the CLP Regulation (EC, 2008)[2] were applied:

Comparison with Category 1 criteria

- *Category 1A (known human carcinogen), known to have carcinogenic potential for humans, classification is largely based on human evidence … The classification in Category 1A … is based on strength of evidence together with additional considerations … Such evidence may be derived from human studies that establish a causal relationship between human exposure to a substance and the development of cancer (known human carcinogen)* (EC, 2008).

There are no epidemiological data to support classification of barium chromate in Category 1A. Epidemiological data like the study of Davies (1984) report that some workers were inter alia exposed to barium chromate. But the strength of the data is not sufficient to provide a clear positive relation between barium chromate exposure and effect. Observed effects in this and other epidemiologic studies are dominated by zinc chromate but not lead chromate exposure. The data for this read-across substance, zinc chromate, clearly indicate a link between an increased incidence of lung cancer and zinc chromate exposure. Therefore, zinc chromate and related substances have been classified as Category 1A carcinogens (ECHA C&L Inventory, 2021; CLP Annex VI, entry 024-007-00-3). 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,

[2] REGULATION (EC) No 1272/2008 considering all ATPs published until June 2021

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.

- *Category 1B (presumed human carcinogen), presumed to have carcinogenic potential for humans, classification is largely based on animal evidence. … The classification in Category … 1B is based on strength of evidence together with additional considerations … Such evidence may be derived from … animal experiments for which there is sufficient evidence to demonstrate animal carcinogenicity (presumed human carcinogen)… In addition, on a case-by-case basis, scientific judgement may warrant a decision of presumed human carcinogenicity derived from studies showing limited evidence of carcinogenicity in humans together with limited evidence of carcinogenicity in experimental animals* (EC, 2008).

Studies in non-standard experimental animals with unknown sensitivity do not show a carcinogenic activity of barium chromate. Only in one rat study with intrapleural application one of 34 rats developed a tumour at the implantation site (Hueper, 1961), whereas no tumours were observed after intrabronchial and intramuscular application. However, very low incidences were also observed under comparable experimental conditions for read-across substances zinc tetrahydroxychromate (tumour in 1/100 rats after intrabronchial application) and zinc chromate (squamous cell carcinomas in 3/100 or 5/100 rats for two different samples of zinc chromate), indicating the limitations of the animal models, which provide only limited evidence of carcinogenicity.

According to section 3.6.2.2.6 of the CLP Regulation *(EC, 2008)* additional criteria should be taken into consideration for the evaluation like information on

- *structural similarity to a substance(s) for which there is good evidence of carcinogenicity,*
- *mode of action and its relevance for humans, such as …mutagenicity.*

In addition, according to section 3.6.2.2.7, a substance that has not been tested for carcinogenicity may in certain instances be classified in Category 1A, Category 1B or Category 2 based on tumour data from a structural analogue together with substantial support from consideration of other important factors such as formation of common significant metabolites, e.g. for benzidine congener dyes.

As outlined above structural similarity and/or formation of the common significant metabolite chromate comparable to other poorly water-soluble carcinogenic chromates classified as carcinogenic category 1A or 1B and the observation

- that barium chromate induces mutagenic effects *in vitro* comparable to the effects observed with other (carcinogenic) chromates,
- that barium chromate leads to an increase of intracellular chromium concentrations *in vitro* quantitatively comparable to the effect of zinc chromate,
- that barium chromate shows transformation activity, however with lower potency, like e.g. zinc chromate,
- that barium chromate causes changes in the concentrations of macrophages and neutrophils in the bronchoalveolar lavage fluid similar to the effects observed with other (carcinogenic) chromates,
- that chromate is systemically available and excreted via the urine after inhalation exposure to barium chromate suggesting local exposure in the lung,

indicate that barium chromate is able to reach cells of local target organs and exert effects there comparable to other chromates including the evenly poor soluble zinc chromates. Therefore, a classification as carcinogen category 1B is suggested for barium chromate.

Comparison with Category 2 criteria

- *Category 2 (suspected human carcinogen): The placing of a substance in Category 2 is done on the basis of evidence obtained from human and/or animal studies, but which is not sufficiently convincing to place the substance in Category 1A or 1B, based on strength of evidence together with additional considerations …. Such evidence may be derived either from limited evidence of carcinogenicity in human studies or from limited evidence of carcinogenicity in animal studies* (EC, 2008).

As outlined above there is no clear evidence for carcinogenic effects of barium chromate in humans and therefore, no classification in Category 1A is suggested. However, the consistency of effects observed for barium chromate and other carcinogenic chromates in mutagenicity studies, cell transformation studies, investigations on intracellular bioavailability, induction of local macrophage reactions in the lung provide evidence that a classification in category 1B like the other chromium-VI compounds is appropriate. Due to the strength of evidence for a category 1B classification no classification as suspected human carcinogen (Category 2) is recommended.

11.9.3 Conclusion on classification and labelling for carcinogenicity

Based on the available information for barium chromate, which reveals its similarity to other carcinogenic chromates, especially under consideration of mechanistic information,

a classification for carcinogenicity (Carc. 1B, H350) is warranted for barium chromate.

As there is no information regarding the carcinogenicity of barium chromate via other routes of exposure and as the classification of zinc chromates is not restricted to the inhalation route, the classification is applicable to all routes. In addition, as the zinc chromates are classified without a specific concentration limit (SCL), also no SCL is proposed for barium chromate.

11.10 Reproductive toxicity

11.10.1 Adverse effects on sexual function and fertility

There are no studies investigating effects of barium chromate or sparsely soluble chromates like e.g. zinc chromate, strontium chromate, zinc potassium chromate or pentazinc chromate octahydroxide on sexual function and fertility. Only studies with highly water-soluble chromates like sodium dichromate, potassium dichromate or chromium trioxide are available which are not representative for barium chromate (for justification see section 10).

11.10.2 Short summary and overall relevance of the provided information on adverse effects on sexual function and fertility

Evaluation is not possible in the absence of studies.

11.10.3 Comparison with the CLP criteria

In the absence of studies on potential effects on sexual function and fertility of barium chromate or possible read-across substances the classification for effects on sexual function and fertility cannot be assessed.

Therefore, no classification for effects on sexual function and fertility is proposed for barium chromate.

11.10.4 Adverse effects on development

There are no studies investigating effects of barium chromate or sparsely soluble chromates like e.g. zinc chromate, strontium chromate, zinc potassium chromate or pentazinc chromate octahydroxide on development.

Only studies with highly water-soluble chromates like sodium dichromate, potassium dichromate or chromium trioxide are available which are not representative for barium chromate (for justification see section 10).

11.10.5 Short summary and overall relevance of the provided information on adverse effects on development

Evaluation is not possible in the absence of studies.

11.10.6 Comparison with the CLP criteria

In the absence of studies on potential developmental effects of barium chromate or possible read-across substances the classification for effects on development cannot be assessed.

Therefore, no classification for effects on developmental is proposed for barium chromate.

11.10.7 Adverse effects on or via lactation

There are no studies investigating effects of barium chromate or sparsely soluble chromates like *e.g.* zinc chromate, strontium chromate, zinc potassium chromate or pentazinc chromate octahydroxide on lactation. Only studies with highly water-soluble chromates like sodium dichromate, potassium dichromate or chromium trioxide are available which are not representative for barium chromate (for justification see section 10).

11.10.8 Short summary and overall relevance of the provided information on effects on or via lactation

Evaluation is not possible in the absence of studies.

11.10.9 Comparison with the CLP criteria

In the absence of studies on potential effects on of via lactation for barium chromate or possible read-across substances the classification for effects on or via lactation cannot be assessed.

Therefore, no classification for effects on or via lactation is proposed for barium chromate.

11.10.10 Conclusion on classification and labelling for reproductive toxicity

In the absence of studies for reproductive toxicity of barium chromate or possible read-across substances no classification for reproductive toxicity is proposed for barium chromate.

11.11 Specific target organ toxicity-single exposure

Evaluation not performed for this substance.

11.12 Specific target organ toxicity-repeated exposure

Evaluation not performed for this substance.

11.13 Aspiration hazard

Evaluation not performed for this substance.

12 EVALUATION OF ENVIRONMENTAL HAZARDS

Evaluation not performed for this substance.

13 EVALUATION OF ADDITIONAL HAZARDS

Evaluation not performed for this substance.

14 ADDITIONAL LABELLING

Not applicable for this evaluation.

15 ANNEXES

Please see separate documents for non-confidential and confidential Annex I.

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