Committee for Risk Assessment (RAC)

Committee for Socio-economic Analysis (SEAC)

Annex to the Background document

to the Opinion on the Annex XV dossier proposing restrictions on
cobalt sulphate; cobalt dinitrate; cobalt dichloride; cobalt carbonate; cobalt di(acetate)

IUPAC Name	EC/List number	CAS number
cobalt sulphate	233-334-2	10124-43-3
cobalt dichloride	231-589-4	7646-79-9
cobalt dinitrate	233-402-1	10141-05-6
cobalt carbonate	208-169-4	513-79-1
cobalt di(acetate)	200-755-8	71-48-7

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12 March 2020

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Annex A: Manufacture and uses

A.1. Manufacture, import and export

A.1.1. Overview of industry

Cobalt salts are both manufactured and imported into the EU (ECHA (2011a) (2011b) (2011c) (2011d) (2011e)). Table 1 provides further details on the location of facilities that manufacture and/or import the cobalt salts (above 1 tonne per annum).

Table 1: Overview of locations for cobalt salt facilities in the EU

Cobalt salt	**EEA member states with facilities either manufacturing and/or importing the cobalt salts**
Cobalt sulphate	Belgium, Finland, Germany, Norway and the United Kingdom (the Netherlands, 2010d; ECHA, 2011d).
Cobalt dichloride	Belgium, Finland, France and the United Kingdom (ECHA, 2011e)
Cobalt dinitrate	Belgium, France, Germany, and the United Kingdom (the Netherlands, 2010b, ECHA 2011b)
Cobalt carbonate	Belgium, Finland, Germany, Norway, and the United Kingdom (the Netherlands, 2010c; ECHA, 2011c)
Cobalt di(acetate)	Belgium, Finland, France and the United Kingdom (Netherlands, 2010a; ECHA, 2011a)

The table below (Table 2) is based on data from the Cobalt Institute (eftec, 2018a) and highlights that there are approximately 30 manufacturing or importing sites in the EU for the cobalt salts. Associated with these, there are around 5 300 workers, of which around 30% (1600) are exposed to the cobalt salts.

Table 2: Number of sites and workers for manufacture/import in the EU (eftec, 2018a)

	Estimate	**Mean (range) per M/I**
Number of manufacturers / importers (M/I)	30	-
Total volume manufactured / imported	37 400 tonnes	-
Total volume manufactured	36 800 tonnes	1 250 tonnes (<10-7 600)
Total volume used in the EU	30 000 tonnes	-
Total number of workers exposed	1 600 (30%)	50 (<10-200)
Total number of workers employed	5 300	180 (10-750)
Note: Tonnage and worker numbers have been rounded to the nearest 100 to avoid impression of false accuracy		

Information regarding the volumes of manufacture/import for each of the individual compounds is not available. Table 3 below summarises the latest information on registered tonnage for each cobalt salt as of February 2018.

Table 3: Registered tonnage bands for the five cobalt salts (February 2018)

Substance name	EC/List number	Registered tonnage band
Cobalt sulphate	233-334-2	10 000 - 100 000 tonnes
Cobalt dichloride	231-589-4	1 000 - 10 000 tonnes
Cobalt dinitrate	233-402-1	100 - 1 000 tonnes
Cobalt carbonate	208-169-4	1 000 - 10 000 tonnes
Cobalt di(acetate)	200-755-8	1 000 - 10 000 tonnes

As set out in Table 2, 37 400 tonnes of the cobalt salts were manufactured in, or imported into, the EU (eftec, 2018a). It can be seen that the majority of this tonnage was manufactured in the EU, with only 600 tonnes being imported. Following exports, the total volume of the cobalt salts placed on the EU market or used internally in the EU is estimated at 30 000 tonnes (implying exports of 7 400 tonnes).

A.1.2. Description of the manufacturing process and the identified uses

The manufacturing process to produce individual cobalt salts has been described in ECHA background documents (ECHA, 2011a, b, c, d, e) and in the registration dossiers. A summary of the manufacturing processes for the cobalt salts is provided in Table 4 below.

Table 4: Manufacturing processes for the five cobalt salts

Cobalt salt	Manufacture process
Cobalt di(acetate)	Production involves dissolving cobalt-containing raw materials including different cobalt compounds or powdered cobalt in acetic acid, followed by hydrometallurgical purification of the solution by precipitation, filtration and solvent extractions, followed by further processing through crystallization, precipitation, filtration and drying. Hydrometallurgical operations are performed in chloride, sulphate or mixed medium. The commercial product is manufactured and sold in the tetrahydrate form of the compound (Patnaik, 2002) cited in ECHA, 2011a). It can be also prepared, by reflux of acetic acid solutions in the presence of cobalt oxide, or by oxygenation of hot acetic acid solutions over cobalt metal (Kirk-Othmer, 2010 cited in ECHA, 2011a).
Cobalt dichloride	Production involves the solubilisation of cobalt-containing raw materials with hydrochloric acid. France also reports that, cobalt dichloride is produced by refining mattes of nickel, with the final steps of nickel extraction, generating cobalt dichloride (France, 2008, cited in ECHA, 2011e).
Cobalt sulphate	Production involves dissolving cobalt-containing raw materials in sulphuric acid, followed by hydrometallurgical purification of the solution by precipitation, filtration and solvent extractions. The purified cobalt solution is further processed using hydrometallurgical operations like crystallization, precipitation, filtration and drying. Hydrometallurgical operations are performed in chloride, sulphate or mixed medium. Crystallization yields the commercial product, pink heptahydrate (Pantaik, 2002, cited in ECHA, 2011d).

Cobalt salt	Manufacture process
Cobalt carbonate	Two different production routes are described. The registration dossiers describe a production process involving selective solvent extraction of cobalt from a mixed nickel and cobalt-containing solution. The cobalt carbonate solution is then neutralised and recovered, after decantation and filtration, as a purple powder. The ECHA (2011c) background document describes a production process involving the addition of a hot solution of cobalt salts to a hot sodium carbonate or sodium bicarbonate solution. Precipitation from cold solutions gives a light blue unstable product. Dissolution of cobalt metal in ammonium carbonate solution followed by thermal decomposition of the solution gives a relatively dense carbonate (Kirk-Othmer, 2010, cited in Netherlands, 2010c).
Cobalt dinitrate	The registration dossiers describe a production process involving the production of a nitrate nickel/cobalt solution by addition of nitric acid to cobalt and nickel chips. This solution is then filtered and the concentration adjusted by addition of cadmium nitrate solution. Caustic soda is added to produce a nickel/cobalt/cadmium di-hydroxide active material. It should be noted this is used in the manufacturing of battery electrodes. According to the ECHA (2011b) background document, cobalt dinitrate can be prepared by dissolution of the simple oxide or carbonate in nitric acid, but more often it is produced by direct oxidation of the metal with nitric acid (Kirk-Othmer, 2010, cited in Netherlands, 2010b).

A.1.3. Waste management and recycling

A report commissioned by the CoRC (Arche, 2015) compiled information from manufacturers, refiners and processors of cobalt and cobalt compounds, on the type of waste streams, amounts of waste produced, composition and management options. This included waste from manufacture of cobalt, waste occurring because of the use of cobalt, and waste formed at the end of service life of articles in which cobalt is contained (Arche, 2015). Based on the information collected, by default it was assumed that all industrial waste is categorized as hazardous and is disposed of via hazardous landfill or hazardous waste incineration (Arche, 2015).

Recycling of catalysts and batteries is carried out by the cobalt industry (Arche, 2015). Industry consultation indicate that, in most industrial processes, there will be a financial incentive to recover cobalt for reuse in the system. Many companies in their (confidential) responses to the ECHA call for evidence have indicated that cobalt-containing catalysts (e.g. hydrotreating catalysts) are either regenerated and rejuvenated for re-use, or completely recycled at the end of their effective lifetime.

A number of downstream users, using cobalt di(acetate) as an oxidation catalyst, for example in the production of terephthalic Acid (PTA) and isophthalic acid IPA, indicate there is a recovery/recycling process for the cobalt salts used as catalysts in this process. The sector trade association CPME indicate that the recovery process involves the separation of the cobalt-rich liquor from the crude product and a conversion/recovery step in which cobalt is recovered as oxalate. Downstream users interviewed indicated that conversion back to cobalt salts is carried out by external professionals. It is indicated that the process also results in waste sludge containing relatively minor levels of impurities of cobalt, which can include soluble and insoluble forms of cobalt. The CPME indicate that the very minor (<10 ppm in final product) amount of cobalt that leaves the system is in the form of insoluble cobalt terephthalate. This waste is typically sent to the municipal waste water treatment works. There is some uncertainty regarding exactly how the cobalt-containing waste is treated in waste water treatment works.

One company (pers. comm., 11/01/18) using cobalt di(acetate) as an oxidation catalyst to produce bio-based intermediate chemicals from high oleic-content vegetable oils, reported that the catalyst can be recovered from waste. Cobalt content in waste is expected to be low (1-2%). In this process, the catalytic water, containing the exhausted catalysts concentrated under vacuum, reduces the water content in the solution from 96% to 10%. The concentrated recovered catalyst is then collected and sent to external companies specialised in the treatment of waste. The company reported that they are developing a method to obtain a cobalt di(acetate) water solution with a concentration of the active ingredient comparable to the concentration in the product that is supplied to them (6.5% Co). The company estimate that currently 30% of cobalt di(acetate) is recycled, with a goal of increasing this proportion to 60%. The company notes that they are actively investigating new ways to improve recovery of the cobalt di(acetate) as this is currently not economically viable to a large degree. It is estimated this will require more than four years of R+D and then a longer period to develop commercially.

One company (pers. comm.,18/01/18) , using cobalt salts in battery electrodes, note that batteries from cell phones, cars, laptops, etc. can be collected at the end of their useful life and the cobalt-containing electrodes recycled via a leaching unit[1] at the plant and the cobalt reused.

In the hard metal sector, one company (pers. comm., 17/01/18) report a process in place for the recycling of cobalt carbonate. In this process, hard metal scrap (e.g. sintered parts, coated inserts, used tools, dies, rolls, off spec material, etc) is mechanically crushed and then undergoes recycling through either mechanical (e.g. zinc, coldstream process) or chemical (chlorination, oxidation, alkaline leaching, electrolytic, acidic leaching, nitrate/carbonate and melting) means to recover the cobalt carbonate.

In the surface treatment process one trade association (pers. comm., 15/01/18) indicated in an interview that the cobalt salts react and are no longer present in the final product. One company (pers. comm., 11/01/18) note that the cobalt in metal component is recyclable and is typically returned to the supplier for recovery and reuse. ZVO (2011) report that, by adjusting the pH value to the alkaline range, cobalt can be precipitated out as cobalt hydroxide at < 1 mg/L. The cobalt salts themselves are not regenerated or recovered. Cobalt in salt form will be treated as chemical waste.

In the use of cobalt dichloride in humidity indicator cards (HICs), it is indicated there is no formal recycling of the cobalt dichloride. It is noted by industry that there is a logistical issue of having a substantial (of the order of thousands) of different users and specific applications. It is also indicated by HIC manufacturers that HICs are typically encased or housed within another structure, for example use in locomotive brake systems. Therefore, if a component is changed and replaced, the old component will be disposed of/recycled with the HIC inside. The levels of release/reuse of cobalt dichloride in this sector are unknown.

A.2. Uses

A.2.1. Overview of uses

Cobalt salts are used in a variety of industrial sectors within the EU. Due to the different properties of each of the salts, they are each used in specific applications which are

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[1] A specific reaction unit where a process for enhancing recovery of cobalt, from spent catalysts when the spent catalyst is carried out. For example, this process can involve the spent catalyst material being heated to between 400° C and 600° C. and then contacted multiple times with a an aqueous solution of ammonia and an ammonium salt to recover cobalt.

summarised in Table 5[2]. Total quantities of cobalt salts used are small but are often essential to the finished product. (CoRC, 2017).

Table 5: Breakdown of main uses of each of the five cobalt salts (compiled from the exposure scenarios)

Sector / Uses	**Cobalt di(acetate)**	**Cobalt dichloride**	**Cobalt sulphate**	**Cobalt carbonate**	**Cobalt dinitrate**
Intermediate uses					
Manufacture of chemicals					
Manufacture of chemicals	X	X	X	X	X
Manufacture of cobalt carboxylates and resinates		X			X
Manufacture of batteries					
Manufacture of cobalt compounds used in batteries			X		X
Manufacture of catalysts					
Manufacture of other cobalt compounds during catalyst production				X	X
Manufacture of pigments and dyes					
Manufacture of inorganic pigments, frits, ceramic ware, glass	X	X	X	X	
Manufacture of dyes for textile, leather, wood and paper industry$^{1)}$	X	X	X		
Non-intermediate uses					
Use as catalysts					
Use as catalyst	X		X		
Use in surface treatment					
Formulation of metal surface treatment pre-formulations	X	X	X	X	X
Passivation process in surface treatment	X	X	X	X	X
Plating process in surface treatment	X	X	X	X	X
Use as colorant					
Use as colorant in the production of PET $^{1)}$	X				
Use in biotechnology					

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[2] The uses are compiled from the exposure scenarios of the registration dossiers (CoRC 2018). Some uses are no longer in place.

Sector / Uses	Cobalt di(acetate)	Cobalt dichloride	Cobalt sulphate	Cobalt carbonate	Cobalt dinitrate
Formulation and use of mixtures in biogas production	X	X	X	X	X
Professional use in biogas production	X	X	X	X	X
Use in fermentation processes, in biotech and scientific research and standard analysis 2)	X	X	X	X	X
Formulation of fertilizers 1) and/or feed grade materials	X	X	X	X	
Bespoke uses					
Use in humidity indicators cards, plugs and/or bags with printed spots		X			
Formulation and use of water treatment chemicals, oxygen scavengers, corrosion inhibitors		X	X	X	X

Source: CoRC (2018): Exposure scenarios from the registration dossiers
1) These uses are understood not to be taking place in the EU at present
2) May include some intermediate uses

Based on a survey conducted by industry in 2014/2015 (CoRC, 2017), the main use of the cobalt salts based on tonnage is as intermediates in the manufacture of chemicals (26 600 tonnes) and catalysts (1 700 tonnes). Other sectors such as surface treatment and biotechnology present much lower volumes.

Table 6: Overview of the volumes and uses of the five cobalt salts in the EU (CoRC, 2017)

Sector	Total volume used in EU (tonnes 2011-2013)	% used as intermediates
Manufacture of chemicals	26 600	100%
Manufacture of batteries 1)	-	-
Manufacture of catalysts	1700	100%
Manufacture of pigments and dyes	<<100	No data
Use as catalyst	800 2)	0%
Use in surface treatment	500	20% 3)
Use as colorant	No data	No data
Use in biotechnology	400	23%
Bespoke uses	<<100	0%
Total	~30 000	~85% of total volume is used as intermediates

Source: CoRC (2017) (adapted by the Dossier Submitter)
1) Volumes included in the manufacture of chemicals
2) Data disaggregated from the production of catalysts
3) Based on information provided by CoRC (2017), 100 tonnes (20% of the volume used in the sector) are used as intermediates in surface treatment. This information is disregarded as it has not been found any further evidence of intermediate use in surface treatment.

Note: Volumes rounded to the nearest 100 tonnes

According to industry (CoRC, 2017), around 70% of the cobalt salts are used in the EU as transported isolated intermediates (mainly in the manufacture of chemicals) while 15% are used as non-isolated or on-site isolated intermediates and are therefore outside the scope of the restriction. However, these figures may be somewhat lower as some uses identified by industry as intermediates, e.g. in the surface treatment sector, are not considered as intermediate uses by the Dossier Submitter.

A.2.2. Manufacture of chemicals

The majority of the use of the five cobalt salts is in the chemicals sector for producing other cobalt-containing substances, such as other inorganic cobalt compounds and cobalt carboxylates. The cobalt salts are used as intermediates in the manufacture of other substances and the estimated annual tonnage of all cobalt salts used across this sector in the EU is 26 600 tonnes (as shown in Table 8 above). Cobalt dichloride (97%), cobalt sulphate (90%) and cobalt carbonate (70%) are all used in the largest volumes in the production of other chemicals. Cobalt dinitrate (~30%) and cobalt di(acetate) (~5%) are both reportedly used at significantly lower levels (RCOM, 2011).

A.2.3. Manufacture of batteries

Cobalt dinitrate and cobalt sulphate (to a less extent) are used as intermediates in the manufacture of rechargeable batteries for the automotive market and for storage applications (The Netherlands, 2010b). Cobalt dinitrate and cobalt sulphate are transformed into cobalt hydroxide or tricobalt tetraoxide which are further used in the manufacture of cathodes for nickel-based batteries (NiCd and Ni-MH) and for lithium ion batteries (LICoO2, NMC or NCA). The use of cobalt compounds in the manufacture of nickel-based batteries is expected to remain stable. However, as the transition to low-carbon transport options occurs, more electric vehicles and plug-in hybrid vehicles are expected to be deployed and the use of cobalt compounds in the manufacture of lithium ion batteries is expected to rise in tandem.

According to industry, the demand of cobalt salts in the future for this sector is expected to double the size of the current market (CoRC, pers. comm., 7/06/2018). The EU battery industry has announced plans for expansion of capacity and for recycling of future supplies of batteries at their end life (10-15 year lifetime) to recover the cobalt content. At present there are more than 20 plants identified in Europe that manufacture cells for these batteries and about 10 plants with capacity to recycle them (CI, 2018). This represents a number of direct jobs estimated at more than 7 000 people. No data has been made available to the Dossier Submitter regarding the volumes of cobalt salts used in this sector.

A.2.4. Manufacture of catalysts

Overall, approximately 8% of the total tonnage of the five cobalt salts are used in catalyst production as intermediates (CoRC, 2017). According to information reported by the trade association ECMA, over the period 2011-13, around 1 700 tonnes of the cobalt salts were used as an intermediate for catalyst manufacture.

The two principal cobalt salts used in the production of catalysts are cobalt carbonate and cobalt dinitrate (CoRC, 2017). One company (confidential, CfE 498) also report the use cobalt sulphate (less than 1 tonne per year) in the manufacture of catalysts. Data from ECMA (CfE 505) suggest the cobalt salts are used as intermediates which are chemically transformed to produce catalyst precursors or active catalyst substances at 11 sites in Europe. Cobalt-based catalysts are mainly used in oil refining (hydroprocessing catalysts), and in Gas-to-Liquid processes where natural gas is converted into longer-chain hydrocarbons (ECMA, CfE 505)The cobalt salts themselves are not present in the final catalyst product.

A.2.4.1. Production of catalysts for hydrotreating/desulphurisation (oil refining)

The main application of cobalt salts (cobalt carbonate and cobalt dinitrate) in the catalyst sector is for use as intermediates for the manufacture of hydrotreating catalysts (ECMA CfE 505). One company (CfE 509) note that most of their cobalt catalyst formulations are based on the use of a combination of cobalt carbonate and cobalt dinitrate, with a ratio between cobalt carbonate versus cobalt dinitrate used in their production of around 70/30.

Refinery catalysts represent a market share of about 25% of a total catalyst market and hydroprocessing catalysts account for approximately 28% of this total refinery catalyst market (ECMA, CfE 2017). However, it should be noted that 'hydroprocessing' encompasses a wide range of processes (e.g. hydrodesulphurisation, hydrodenitrogenation, hydrodeoxygenation, etc).

According to the call for evidence response (see annex G) submitted by ECMA, the use of cobalt-containing catalysts is essential to produce clean transport fuels and help guarantee that fuels meet the low sulphur standards needed to avoid sulphur emissions leading to acid rain (ECMA, CfE 505). Therefore, the focus on reducing sulphur content of fuels suggests a likely increasing demand and market for cobalt-containing desulphurisation catalysts in the future.

A.2.4.2. Production of catalysts for Gas to Liquid (GTL) (Fischer-Tropsch)

The key catalytic reaction in the GTL process is the conversion of carbon monoxide and hydrogen into hydrocarbons of various chain lengths (Fischer-Tropsch).Only a limited number of Gas-to-Liquid facilities are in operation and the cobalt salts (cobalt carbonate and dinitrate) reportedly form an essential part of the gas to liquid conversion process. It is estimated that the volume of cobalt catalysts needed for starting a plant is from 100 – 600 tonnes cobalt depending on the type and size. Once started the yearly supply is however much lower, roughly estimated 110-150 tonnes per annum (ECMA, CfE 505).

A.2.5. Manufacture of pigments and dyes

Based on information provided by industry (CoRC, 2017) the use of the cobalt salts in the manufacture of pigments and dyes is a relatively minor use, estimated at significantly less than 100 tonnes per year representing less than 1% of the uses of the cobalt salts.

A.2.5.1. Manufacture of dyes for textile, leather, wood and paper industry

Cobalt sulphate, cobalt dichloride and cobalt di(acetate) (to a lesser degree) are used as the starting material for the synthesis of dye compounds used in textiles. During the synthesis of the dyes the cobalt salt entirely converted into a 2:1 metal complex dye whereby to dye molecules are attached to a single metal atom. Thus there is no presence of the cobalt salt in the final dye. The production of dyes has decreased significantly in the past 25 years in the EU, USA and Japan, while it has significantly increased in Asian countries (CDI, 2016).

No information is available regarding the use of the cobalt salts in the manufacture of dyes for the leather, wood and paper industry, although these uses are currently identified in the exposure scenarios of the registration dossiers (CoRC, 2017).

A.2.5.2. Manufacture of inorganic pigments, frits, ceramic, ware and glass

The cobalt salts are reportedly used (along with other raw materials) to make driers and pigments and in pre-formulation in coatings, inks, paints, ceramics, coloured roof tiles, decorative porcelain, and glass. However, more recent information from industry (CI/CoRC, pers. comm., 08/03/2018) indicated that, while these uses are included in the exposure scenarios (CoRC, 2018) they may not exist any longer.

In the call for evidence conducted to collect information for the development of the restriction dossier (see annex G), cobalt sulphate has been reported to be used as an intermediate in the production of white zinc sulphide pigment (CfE 512). According to the information provided by one manufacturer, cobalt sulphate is transformed into cobalt sulphide and is not present in the final product.

A.2.6. Use as catalysts

Cobalt salts are used as catalysts directly without processing or manufacture of precursors. According to data provided by industry (CoRC, 2017), cobalt di(acetate) is used as an oxidation catalyst in the manufacture of polyester monomers for the polyester sector, including purified terephthalic acid (PTA) and isophthalic acid (IPA). Cobalt di(acetate) is also reported by a trade association (pers. comm., 11/01/18) as being used as a co-catalyst in the manufacturing process of polyethylene terephthalate (PET) itself. It was estimated that the use of cobalt di(acetate) catalyst is ~750 tonnes/year, of which ~80% is used for PTA and IPA manufacture. The CPME suggested this figure may now be lower due to the closure/inactivity of some plants. It was indicated that cobalt di(acetate) was used in the production of DMT (dimethyl terephthalate) but this use is no longer in place.

In the call for evidence, one company (CfE 493) also report the use of cobalt sulphate (4 to 5 tonnes per year) as a catalyst in their manufacturing process. No further information is available regarding this use.

A.2.7. Surface treatment sector

The total volume of cobalt salts used in the surface treatment sector in the EU (2011-2013) was 500 tonnes, representing 1.5% of the total usage of cobalt salts in the EU.

The most comprehensive information regarding the volumes used in this sector has been provided by the Central Association of Surface Treatment Professionals Germany (ZVO). Additional information has been collected in interviews with the ZVO in preparation of the present analysis, and with individual companies, along with the information submitted in the call for evidence for the preparation of this restriction dossier.

According to ZVO (pers. comm., 15/01/18), cobalt sulphate and cobalt dinitrate are the most commonly used cobalt salts in the surface treatment sector, with some use of cobalt di(acetate). It is indicated that cobalt carbonate and cobalt dichloride are not widely used due to difficulties with handing and issues of corrosion respectively.

The main uses of cobalt salts within the surface treatment sector are described below [3].

A.2.7.1. Formulation of surface treatment solutions

The solutions used in the surface treatment processes are produced, typically by dissolving solid-phase components in water. The formulation of cobalt salt solutions can take place either at specialised formulators or at large scale surface treatment units. It is to be noted that small scale formulators of surface treatment solutions have not been identified (ECHA, 2017 a).

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[3] It should be noted that other uses in the surface treatment sector (e.g. target material in X-ray tubes, colour baths) have been identified, however no information on these uses has been provided by downstream users interviewed or in the ECHA call for evidence so these uses are not discussed in this report.

A.2.7.2. Passivation

The cobalt salts are used in the generation of 'conversion layers' (also called passivation) typically on zinc- or zinc alloy-coated metallic products for corrosion protection[4]. Conversion layers delay the initial attacks on the metallic protective layer made of zinc or zinc alloy. For this reason, they are used mainly for improving the corrosion resistance of zinc plated metal, hence leading to longer service life and operating time of metal components, particularly in the automotive industry.

Historically, the use of Cr(VI) in the surface treatment sector has been phased out in favour of Cr(III) in many cases. However, industry indicates that Cr(III)-based conversion coatings can only achieve high levels of corrosion protection if cobalt (II) salts are added to the application solutions, typically in proportions of < 2% with reference to the conversion layer (ZVO, 2011). In this process the galvanized components are dipped in a treatment solution containing trivalent chromium compounds and a proportion of cobalt salts. The cobalt-containing solutions react chemically with the metal surface and generate thin conversion layers approx. 30 to 1 000 nm thick. The cobalt ions are integrated into the surface as oxides or as spinels. The addition of cobalt salts is necessary if corrosion protection is required in warm or hot environments (e.g. engine spaces, brakes, gearboxes and in electrical parts in housings, etc.).

One company (CfE 518) estimates that around 45% of the components cobalt-coated by galvanising companies in Germany are used in the automotive sector. Cobalt salts also have important applications in the aerospace and defence sectors as well as in window construction (CfE 490 and CfE 518).

A.2.7.3. Plating

The cobalt salts are used in metal or metal alloy plating (mainly gold-cobalt and tin-cobalt plating) for increased hardness and wear resistance and/or for metal colouring.(ECHA, 2017a).

Plating is a similar process to passivation but electrical current is used to form the surface. Cobalt salts are added to solutions of other metals (e.g. nickel, tungsten, iron, molybdenum, chromium, zinc, and precious metals) to form alloys in electroplating. During the plating process the cobalt substances are transformed into cobalt metal. For example in gold-cobalt electroplating, gold and cobalt are formed and deposited concurrently building a surface coating of gold alloy. These alloys have improved properties (e.g. hardness, wear resistance) compared to gold on its own.

Metallic alloy coatings produced by electroplating are used for example in the jewellery and the watchmaking industry (CfE 513).

A.2.8. Use as a colorant

Cobalt di(acetate) has historically been used as a pigment for PET manufacture, but it is understood that this use has now ceased in the EU (pers. comm., 11/01/18) , though it may still be used for PET manufactured outside of the EU (CoRC, 2017).

A.2.9. Biotechnology (and health) sector

The use of cobalt in the biotechnology sector is primarily due to its functionality as an essential element in plant and animal species. Cobalt is essential to produce vitamin B12 and therefore

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[4] One company also reports the use of cobalt salts in producing protective oxidised coatings on aluminium surfaces.

has multiple applications across the biotechnology and health sector (CoRC, 2017). Downstream users use cobalt salts as well as other raw materials to make their various biotechnology products, such as feeds for livestock; alternative energy from biogas; and technical enzymes, medicines and vitamins (eftec and wca, 2015). The two biggest uses of cobalt salts in the biotechnology sector are biogas and animal feeds. The other two specific uses (fermentation and biotechnological processes; and health and medicines) encompass small volumes (i.e. significantly less than 0.01 tonne per year for most companies).

The estimated annual tonnage of cobalt salts used was 400 tonnes between 2011-2013 (CoRC, 2017), contributing less than 1.5 % of the total volume of cobalt salts used across all sectors. However, the introduction of Regulation (EU) No 131/2014 concerning the authorisation of the use of cobalt salts as feed additives has limited the use of cobalt in this sector recently and led to a decline in use. Data collected from the CoRC (2017) now estimates usage to be approximately 200 tonnes based on 2014-2016 data.

A.2.9.1. Animal feeds and fertilisers

In the EU, over 40% of the overall agricultural output is from livestock which requires approximately 450 million tonnes of feed each year (CoRC, 2017). The use of cobalt salts in animal feed is subject to Regulation (EC) no 1831/2003 on additives for use in animal nutrition, which establishes the requirement of an authorisation for this use. Cobalt salts[5] are contained in the form of premixtures within compound feeds (defined as animal feeds containing supplements). Around 300 units formulate cobalt-containing preparations or premixtures in the EU while compound feeds are manufactured in approximately 4 100 sites (CDI, 2012). The amount of cobalt salts used in the feed sector in 2016 suggest quantities of approximately 200 tonnes per year, made up of 180 tonnes of cobalt carbonate, 20 tonnes of cobalt sulphate and 0.01 tonnes of cobalt di(acetate), all in powder form. Cobalt carbonate is used in the form of coated cobalt carbonate (FEFAC, FEFANA, EMFEMA, CfE 491).

According to information received by industry, (FEFAC, FEFANA, EMFEMA, CfE 491), the use of cobalt salts in the animal feed sector involve several steps:

1) Manufacture of cobalt-containing preparations with a concentration of 2.5 to 10% of cobalt salts (i.e. 1-5% cobalt). The cobalt salts are mixed up with carriers, which can be either sorbitol or glycerol. The purpose is to reduce worker's exposure further down the chain. This operation is performed by specialised companies (no more than five in the EU). At this stage the starting material is cobalt salts in a powder form and the final diluted product is also in a powder form with concentrations of the cobalt salts at 2.5 to 10%, i.e. 1-5% cobalt. In the case of cobalt carbonate (which represents 90% of the use of cobalt salts in this sector) , the formulation is followed by a coating step aimed at reducing workers' exposure at the following stages of the chain. This operation is performed by three companies in the EU. The starting material is cobalt carbonate in powder form and the final product is a preparation of coated granulated cobalt carbonate at concentrations of 1-5% of cobalt.

2) Manufacture of premixtures. The cobalt-containing preparations are mixed up and diluted with other feed additives and carriers and incorporated into a premixture. The starting materials are the preparations of cobalt salts, either in powder form or as coated granulated cobalt carbonate, whereas the final product (i.e. the premixture), is usually in a powder form, sometimes in a liquid form, at concentrations between 0.005 and 0.75%, and more and more below 0.01%.

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[5] Cobalt salts authorised as feed additives at present include cobalt acetate hydroxide, cobalt carbonate and cobalt sulphate

3) Manufacture of compound feed, i.e. either complete feed with concentrations of cobalt at 1 ppm (0.0001%) or complementary feed at levels not exceeding 100 ppm (0.01%). Certain dietetic feed may contain cobalt salts at levels above 100 ppm. Since the introduction of the authorisation requirements in 2014, cobalt-containing compound feed can only placed on the market in non-powdered forms unless it contains coated granulated cobalt carbonate.

4) Professional use (farmers). Farmers use compound feed (complete feed or complementary feed) in different forms (non-powder forms, or powder forms containing coated granulated cobalt carbonate) with a cobalt concentration below the classification limit, i.e. 0.01%. In some cases they may also use specific dietetic feeds, usually in the form of bolus, liquid drenches, or licking blocks, with a cobalt concentration below 0.1%.

Cobalt is also used in fertilisers as a supplement and has a direct impact on food produced within the EU (CoRC, 2017), although it is understood that this use does not apply to any of the five cobalt salts in question. According to the International Food Policy Research Institute (IFPRI), on average, the EU consumes around 16 million tonnes of fertilisers (IFPRI, 2016) regulated under Regulation EC No 2003/2003 on fertilisers. Fertilisers Europe was contacted by ECHA in 2013 and reported that no cobalt salts are used by their members for the manufacture of fertilisers. When contacted again in 2018, Fertilisers Europe provided information to suggest that cobalt carbonate can be added to fertilisers as a micro-nutrient in the form of a chelate or a water soluble complex involving ligands. However, to their knowledge, the cobalt salt is purchased in the form of a chelate, indicating that the use is likely to be covered under chemicals as an intermediate.

Based on discussion with the CI/CoRC (8 March 2018), they have been in contact with the fertilisers industry and could not find any record of current use of any of the five cobalt salts in fertilisers in Europe. To the best of their knowledge there is no use of the five cobalt salts in either formulation or use of fertilisers at present.

A.2.9.2. Fermentation and biotechnological processes

In comparison to the feed sector, fermentation and biotechnological processes use small volumes of cobalt salts as a trace element/micronutrient. Cobalt acts as an initiator or technical enzyme catalyst (CoRC, 2017). Cobalt is also used as an essential element in key fermentation systems to provide the various biological substances needed in the production and development of in-vitro diagnostics (IVD) (CDI, 2012). Cobalt salts are also used as a co-factor for enzymes in kits for IVD and scientific research and to calibrate, control, qualify and validate colour measurement of IVD instruments (CfE 517).

Limited information is available regarding the total amount of cobalt salts used by these sectors. However, one company stated that cobalt salts (cobalt dichloride; cobalt dinitrate; cobalt sulphate – with cobalt dichloride being the main reported use) are used in very small quantities by the IVD sector (e.g. one company reported use of cobalt dichloride from 150g to 200g of crystalline cobalt dichloride per year; another respondent noted that the single uses of cobalt salts do not exceed 25g; CfE 517). This quantity has reportedly remained the same for several years and companies expect that the use will remain the same in the future (CfE 517). The highest consumption reported is around 300kg per year by one individual manufacturing site as a 'feed element' for microorganisms in the fermentation process (ECHA, 2013b). EDMA (European Diagnostic Manufacturers Association) estimate the use of powder forms of cobalt dichloride, dinitrate and sulphate in IVDs to be <0.2 tonnes per year, <0.01 tonnes per year and <0.01 tonnes per year respectively.

A.2.9.3. Health and medicines

Within the health and medicines sector, the cobalt salts play a similar role as in the other biotechnology sectors. Cobalt is used because it is biologically essential and cannot be replaced by another element (CDI, 2012). These applications include the production of medicines and vaccines against major diseases like cancer, diabetes, Crohn's disease and rheumatoid arthritis. Again, although only small volumes are used, cobalt is an essential element in the development of the final medical and healthcare products (CoRC, 2017). No specific information is available on the quantity/tonnage of cobalt salts used in this sector, however eftec (2018a) report the use to be significantly less than 10 tonnes per year in the EU for fermentation, biotech processes, health and medicine sectors combined and Animal Health Europe indicate quantities used per batch are very low (in the range of 10-1000g).

One company (CfE 506), uses cobalt salts (almost exclusively cobalt dichloride) in the manufacturing of pharmaceutical, diagnostic, and research-only products in the European Union and in indirect uses, including purchased cell culture media also containing cobalt salts. Their uses of cobalt salts fall into the following categories: (1) micro-nutrient in fermentation with cell cultures, (2) co-factor for enzymes used in kits for in-vitro diagnostics and scientific research and (3) agent for the modulation of glycolization (a key step in manufacturing) of proteinic active pharmaceutical ingredients, in particular therapeutic antibodies. None of the single uses exceeds 25 g and the total annual amount used is significantly below 1 kg.

An additional UK company (pers. comm., 23/01/11) suggested they use less than 1 tonne per year of cobalt dichloride in solid/powder form as a trace element in the fermentation process in the production of antibiotics, used in animal health products (both feed and therapeutics). Cobalt dichloride is utilised in the fermentation reaction so is not incorporated in the final products.

Cobalt dichloride is also added as a trace element for enzyme fermentations, which are then used in blood testing devices in the UK (pers. comm., 15/01/18). Cobalt dichloride is principally involved in the manufacture of these enzyme fermentations used in blood tests for other medical and life science companies (ultimately hospitals). Adding the salt reportedly makes a significant difference to yield in these enzyme reactions. Quantities of cobalt dichloride in use by this company are estimated to be a maximum of 150-200g per year with a maximum concentration of 0.0005% in finished products.

A.2.9.4. Biogas production

Biogas production is a technology based on the degradation of complex organic materials (such as energy crops, waste, sewage sludge and manure) to produce energy-rich, methane-based gas, called biogas (ECHA, 2013b). Cobalt salts are used in small amounts as a nutrient additive necessary for bacterial cell growth and reproduction in biogas production from energy crops. Cobalt sulphate, cobalt dichloride, cobalt dinitrate, cobalt carbonate and cobalt di(acetate) are all used interchangeably by the biogas industry as a source of cobalt. Total use as reported by industry in 2013 was 97 tonnes, 40 tonnes of which was cobalt carbonate (ECHA, 2013). Since then the biogas industry in Europe has continued to grow from over 13 800 sites in 2012 (Scarponi, 2015) to 17 240 sites in 2015 as reported by CoRC (2017) and EBA (2015). Further information on quantities in use in 2016/2017 has been obtained through stakeholder consultation, suggesting the use in the biogas sector is approximately 130 tonnes. The cobalt salts in this sector are used either in pre-weighted bags (that are used without opening, i.e. thrown in large biomass reactors) or in small amounts (CoRC/CI, pers. comm., 16/03/2018).

A.2.10. Other / bespoke uses

A.2.10.1. Humidity indicators

Humidity indicators can be supplied to the market in a number of formats (e.g. including plugs, cards and indicating silica gel sachets and canisters) (ECHA, 2017).

Humidity indicator cards (HIC) contain chemically impregnated- indicating spots that change colour depending on the level of moisture present. In practice the humidity indicator spots will change (reversibly) from blue (dry condition) to pink (humid condition) as the relative humidity changes.

HICs have a wide range of potential uses in different sectors; specific applications highlighted by the downstream users consulted include use in the electronics industry, industrial and military applications (CfE 503), in the manufacture of sight glasses used for monitoring the humidity in refrigerant systems (CfE 486) and in packaging material for quality assurance transportation of semiconductor devices (microchips) (CfE 499).

Cobalt dichloride paper has been used as an indicator of humidity and moisture for over 70 years (Soloman, 1945). No other cobalt salt is in use for manufacturing HICs (CoRC 2018). According to one company (pers. comm., 12/01/18), the use of other cobalt salts to produce HICs is not considered viable due to performance, costs and/or safety limitations.

Industry stakeholders consulted indicate that the use of cobalt dichloride has ceased for many HIC applications. Most remaining HIC products using cobalt dichloride are connected either directly or indirectly to military specifications (CfE 503). Industry stakeholder interviews indicate <200 kg of cobalt dichloride is used globally in this sector (CfE 503).

One manufacturer of HICs (pers. comm., 12/1/18) indicated that other type of humidity indicators such as silica gel coated in cobalt dichloride has not been manufactured in Europe for approximately 20 years, as most users that need desiccant use either a bentonite clay or silica gel desiccant (in bags, packets or canister packaging form) with a HIC, as this is considered to be the most effective combination.

One respondent from an industry survey conducted by ECHA in June 2018 (see annex G) specifies the use of cobalt salts for manufacturing of moisture indicators for mine rescue devices, where the cobalt salt in powder form is applied to a substrate / gel. The respondent does not specify the final format in which the humidity indicator is placed on the market.

A.2.10.2. Water treatment chemicals

Oxygen scavenger mixtures based on sodium sulphite are capable of reacting with and removing dissolved oxygen from boiler feed water, thus helping to prevent corrosion which might lead to failures of boiler systems (ECHA, 2017). The five cobalt salts discussed except cobalt di(acetate) are used in the formulation and use of oxygen scavengers in this water treatment application. Reported volumes of cobalt salts used as catalyst in oxygen scavenging processes is reported by ECHA (2017) to be 1-10 tonnes per year.

A.2.10.3. Other uses

According to the information provided in the call for evidence (CoRC, 2017), at least one of the cobalt salts (cobalt dichloride) is used in the production of laboratory reference standards in the nuclear energy sector. Nuclear power plants generate almost 30% of the electricity produced in the EU, from 130 nuclear reactors in operation in 14 EU countries. The vast majority of these plants run on uranium fission process, and cobalt-60 is a by-product of this process. Cobalt dichloride is used in the production of laboratory reference standards for calibration of the measurements of radioactive cobalt-60, and these standard laboratory solutions are assumed to be used by all nuclear power plants (and all plants within the nuclear cycle industry) to monitor the gaseous release of cobalt. Similar laboratory reference standards are also used in the medicinal field. There is currently no information on the interchangeability of other cobalt substances for this specific use (CoRC, 2017).

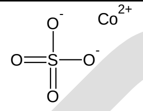
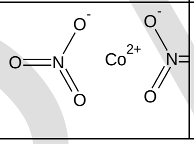
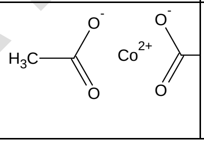
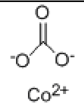
No information is available regarding the volumes of cobalt salts used in this sector of activity although it is expected to be very small. The conditions of use of the cobalt salt in this sector are similar to those in fermentation processes (according to the exposure scenarios of the registration dossiers) and therefore will be discussed within the use in fermentation and biotechnology processes.

Annex B: Information on hazard, exposure/emissions and risk

B.1. Identity of the substance (s) and physical and chemical properties

B.1.1. Name and other identifiers of the substance (s)

Table 7: Substance identity

EC name	**cobalt sulphate**	**cobalt dinitrate**	**cobalt dichloride**	**cobalt di(acetate)**	**cobalt carbonate**
EC number	233-334-2	233-402-1	231-589-4	200-755-8	208-169-4
CAS number	10124-43-3	10141-05-6	7646-79-9	71-48-7	513-79-1
IUPAC name	cobalt(2+) sulfate	cobalt(2+) dinitrate	cobalt(2+) dichloride	cobalt(2+) diacetate	cobalt(2+) carbonate
Molecular Formula	$CoSO_4$	$Co(NO_3)_2$	$CoCl_2$	$Co(C_2H_3O_2)_2$	$CoCo_3$
Structural formula			Cl^- Co^{2+} Cl^-		

The restriction report also covers the hydrated forms of the substances.

B.1.2. Composition of the substance (s)

Cobalt sulphate is an inorganic mono constituent substance usually marketed as cobalt sulphate heptahydrate. Cobalt sulphate is the main component with a typical concentration from 99.7% to circa 100%. Impurities may include nickel sulphate (EC 232-104-9) in concentrations below 0.5%.

Cobalt dinitrate is an inorganic mono constituent substance usually marketed as cobalt dinitrate hexahydrate. Cobalt dinitrate is the main component with a typical concentration from 99.7% to circa 100%. Impurities may include nickel dinitrate (EC 236-068-5) in concentrations below 0.5%.

Cobalt dichloride is an inorganic mono constituent substance usually marketed as cobalt dichloride hexahydrate. Cobalt dinitrate is the main component with a typical concentration from 99.7% to circa 100%. Impurities may include nickel dinitrate (EC 236-068-5) in concentrations below 0.5% and hydrogen chloride (EC 231-595-7) in concentrations below 5%.

Cobalt di(acetate) is an inorganic[6] mono constituent substance usually marketed as cobalt di(acetate) tetrahydrate. Cobalt di(acetate) is the main component with a typical concentration from 99.5% to circa 100%. Impurities may include nickel di(acetate) (EC 206-761-7) in concentrations below 0.6%.

Cobalt carbonate is an inorganic mono constituent substance with cobalt carbonate as the main component in concentrations typically from 97.0% to circa 100%. Impurities may include nickel carbonate (EC 222-068-2) in concentrations below 1.1% and cobalt dichloride (EC 231-589-4) in concentrations below 7.5%.

(The information regarding the composition of the substances has been extracted from the registration dossiers (CoRC, 2018)).

B.1.3. Physicochemical properties

Table 8: Physicochemical properties of the cobalt salts (extracted from ECHA Project SR 23, Larsen *et al*, 2015)

EC name	**cobalt sulphate**	**cobalt dinitrate**	**cobalt dichloride**	**cobalt di(acetate)**	**cobalt carbonate**
EC number	233-334-2	233-402-1	231-589-4	200-755-8	208-169-4
Molecular weight	154.99 (anhydrous) 281.10 (heptahydrate)	182.94 (anhydrous) 291.03 (hexahydrate)	129.84 (anhydrous) 237.93 (hexahydrate)	177.02 (anhydrous) 249.08 (tetrahydrate)	118.94 (anhydrous)
Physical state	Cobalt sulphate heptahydrate is a rose, odourless, crystalline, inorganic solid	Cobalt dinitrate hexahydrate is a red purple, flaked, inorganic solid	Cobalt dichloride hexahydrate is a purple, odourless, crystalline, inorganic solid	Cobalt di(acetate) tetrahydrate is a red, crystalline, inorganic solid	Cobalt carbonate is a red powder or rhombohedral crystals
Melting point	>700°C	Decomposes at about 100 °C. No melting point can be determined	735°C and 737°C	Decomposes around 370 °C. No melting point can be determined	Decomposes at 280 °C.
Relative Density	3.71.	2.49.	3.36 - 3.37.	1.76.	4.2.
Vapour pressure	Negligible, i.e. below the level of significance (10^{-5} Pa)	Negligible, i.e. below the level of significance (10^{-5} Pa)	Negligible, i.e. belowthe level of significance (10^{-5} Pa)	Negligible, i.e. below the level of significance (10^{-5} Pa)	Negligible, i.e. below the level of significance (10^{-5} Pa)
Water solubility	376.7 g/L at 20°C and 391.5 g/L at 37°C	> 669.6 g/L at 20°C	585.9 g/L at RT	348.04 g/L and 360 g/L at 20°C	< 0.022 g/L

B.1.3. Justification for grouping

See report section 1.2.3.

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[6] Cobalt salts with organic anions are considered as inorganic compounds.

B.2. Manufacture and uses

See report section 1.2.5.1 and annex A.

B.3. Classification and labelling

B.3.1. Classification and labelling in Annex VI of Regulation (EC) No 1272/2008 (CLP Regulation)

See report section 1.2.2.

B.3.2. Classification and labelling in classification and labelling inventory/ Industry's self-classification(s) and labelling

Cobalt sulphate:

https://echa.europa.eu/information-on-chemicals/cl-inventory-database/-/discli/details/79319

Cobalt dinitrate:

https://echa.europa.eu/information-on-chemicals/cl-inventory-database/-/discli/details/242

Cobalt dichloride:

https://echa.europa.eu/information-on-chemicals/cl-inventory-database/-/discli/details/119523

Cobalt di(acetate):

https://echa.europa.eu/information-on-chemicals/cl-inventory-database/-/discli/details/126330

Cobalt carbonate:

https://echa.europa.eu/information-on-chemicals/cl-inventory-database/-/discli/details/72255

B.4. Human health hazard assessment

The information in this section is limited to information related to the carcinogenicity effect and the sensitising properties of the cobalt salts. Where appropriate, information related to other cobalt compounds is also considered in the assessment. A brief discussion on the toxicokinetics of cobalt and cobalt compounds is presented herein.

B.4.1. Toxicokinetics (absorption, metabolism, distribution and elimination)

Absorption

Studies describing absorption of cobalt from the respiratory tract are sparse. However an approximately absorption rate of 30 % of inhaled cobalt oxide particles has been found in a study using hamsters (WHO/CICAD, 2006). After inhalation of cobalt and cobalt substances in experimental animals, marked increases of cobalt have been found in the lungs, but increased cobalt levels were also found in the liver, kidney, trachea, spleen, bones and heart with the highest levels in the liver and kidneys (WHO/CICAD, 2006).

Increased levels of cobalt in urine from humans exposed by inhalation to cobalt substances indicate that absorption takes place after inhalation (ECHA Project SR 23, Larsen *et al*, 2015). Deposition in the respiratory tract primarily depends on particle size and breathing patterns. In general larger particles tend to deposit in the upper respiratory tract due to higher airstream and inertial airstream velocities and inertial impaction. These particles are readily cleared through mucociliary action and swallowed. Smaller particles escape inertial impaction and deposit in the bronchiolar or alveolar regions. Particles deposited in the respiratory tract may dissolve and be absorbed into the blood or undergo phagocytosis or endocytosis by macrophages. Recent in vitro studies with human lung cells show that water insoluble cobalt oxide particles (CO or CO_3O_4) are readily taken up through endocytosis and are partially solubilized at the low pH within lysosomes while soluble cobalt salts utilize cellular transporters such as calcium channels or the divalent ion transporter to enter cells (NTP, 2016).

In experimental animal rat studies gastrointestinal absorption of 13-14 % has been found for cobalt dichloride compared to only 1-3 % for the insoluble cobalt oxide. Cobalt dichloride administered together with milk had a significant higher absorption rate of approximately 40% (ECHA Project SR 23, Larsen *et al,* 2015).

In humans, absorption rates of 18 to 97 % of an oral dose have been found depending on type and dose of the cobalt compound and the nutritional status of the individual. The absorption is increased among individuals with iron deficiency as rates of 31-71 % were found compared to individuals without iron deficiency (18-44%) (WHO/CICAD, 2006).

An *in vitro* experiment using human skin determined the dermal absorption using applications of cobalt dichloride of approx. 100 µg/cm² and approx. 1 000 µg/cm² for an exposure duration of 8h. For the two exposure concentrations, the corresponding absorbable doses (sum of absorbed dose and skin and stratum corneum) were calculated to 0.38% and 1.08%, respectively (OECD, 2014).

In an experimental animal study, hamsters exposed to 100 µl of a solution containing 2 µg cobalt chloride/µl on shaved skin eliminated 33 µg of this dose during 48 hours indicating a significant degree of absorption (MAK, 2009).

Increased levels of cobalt in urine has also been determined after dermal exposure of humans to lubricating oil containing cobalt substances (MAK, 2009).

Distribution

Absorbed cobalt is distributed rapidly to all tissues in experimental animals and is similar to that in humans. According to NTP, tissue distribution depends on dose, route of administration and time. Following oral administration of cobalt compounds, the highest tissue concentrations generally occur in the liver and kidney with lower amounts in the heart, spleen, muscle, bone, brain, pancreas, lung and gonads (NTP, 2016). In pregnant rats increased cobalt levels were found in foetal blood and amniotic fluid after oral exposure (WHO/CICAD, 2006).

Distribution of cobalt following inhalation exposure is similar to that observed for other routes with the exception of greater retention in the lung for both soluble and insoluble cobalt. Long-term retention of insoluble cobalt particles and soluble cobalt particles deposited in the lung shows wide interspecies variation and represents a potential continuing source of cobalt ion release. Nanoparticles may also penetrate the alveolar membrane and distribute to extra pulmonary tissues via the circulation (NTP, 2016).

Elimination

In experimental animals, soluble cobalt compounds are absorbed into the blood at a faster rate than less soluble compounds and excreted in the urine and faeces following inhalation exposure. Urinary excretion rates seem to correlate with the translocation rate of cobalt from the lungs to blood, whereas faecal excretion rates seem to correlate with mechanical clearance rates of cobalt from the lungs to the gastrointestinal tract. Following an initial high rate of faecal clearance, urinary excretion is the primary route of cobalt elimination after a single inhalation exposure or 3 months of exposure (WHO/CICAD, 2006).

Following inhalation exposure to insoluble cobalt compounds, a three phase elimination kinetics were observed in humans. The half-life for the first phase, likely representing mucociliary clearance in the tracheobronquial region, was approximately 2 to 44 hours. The second phase with a half-life of approximately 10 to 78 days may represent macrophage-mediated clearance of cobalt particles from the lung. The third phase clearance with a half-life in the order of years may represent long-term clearance of cobalt particles from the lung. Controlled aerosol studies in human volunteers show that about 40% of the initial lung burden of inhaled cobalt oxide particles were retained in the respiratory tract after six months. About 33% of the initial lung burden was found in the urine with 28% in faeces six months after exposure (NTP, 2014).

In experimental animals, faecal elimination is the primary route of excretion following oral exposure. Faecal clearance has been noted to decrease as cobalt particle solubility increases. In several species, oral exposure to cobalt (II or III) oxide (with ^{57}Co tracer) resulted in little gastrointestinal absorption and a rapid elimination in faeces (>96 %). Cobalt dichloride was excreted primarily via faeces (70–83 % of the administered dose) in rats, with urinary excretion accounting for the remainder of the dose. Single exposures in beagle dogs demonstrated that insoluble cobalt (II or III) oxide was eliminated in the faeces and urine at 90 % and 5 %, respectively, while the more soluble cobalt dinitrate was eliminated at 70 % in the faeces and 25 % in the urine (WHO/CICAD, 2006).

In humans, faecal elimination is also the primary route of excretion following oral exposure. Faecal elimination has been found to vary (3–99 % of the dose) depending on the amount and type of cobalt administered and the nutritional status of the subject. Several days after an oral exposure, ten times more cobalt was excreted in faeces than in urine. In subjects with an iron deficiency, less cobalt was eliminated in the faeces, and more was absorbed (WHO/CICAD, 2006).

No information on the elimination of cobalt following dermal exposure is available.

B.4.2. Sensitisation

The five cobalt salts under this restriction proposal have a harmonised classification as Resp sens.1 as well as Skin sens.1 according to CLP. Therefore it is not considered necessary to evaluate the full database with a view to assert the potential of the five cobalt salts to cause sensitisation. Several recently published reports (as summarised below) confirm that cobalt salts have adverse sensitising effects on the respiratory tract and on the skin.

Some epidemiological studies conducted in cobalt-producing facilities support the findings that occupational exposure to cobalt compounds is associated with occupational asthma. Specifically, studies have shown that there was a significant correlation between decreasing lung function tests (FEV1/FVC ratio) and increasing concentrations of cobalt in the air and urine of occupationally exposed workers (SWH, 2005b).

In a study carried out by Sauni *et al* (2010) in a Finnish cobalt plant with approximately 700 workers, 22 cases of cobalt were diagnosed between 1967 and 2003. The incidence of cobalt asthma was the highest in the departments with the highest cobalt exposure levels and simultaneous exposure to irritant gases. The only department where no asthma cases were found was the chemical department where no irritant gases where present. According to the authors an irritant effect of gaseous compounds may enhance the risk of cobalt asthma and even the smallest amounts of cobalt may be harmful to susceptible workers.

Several assays for skin sensitisation in mouse lymph node assay (LLNA) show that cobalt salts are potential skin sensitisers. Both available animal and human data confirm the skin sensitisation potential of cobalt salts. Cobalt dichloride is a strong skin sensitiser (grade 5 of 5 in the guinea-pig maximisation test) (Fischer *et al*, 2016).

A number of studies show the skin sensitization potential of the cobalt salts in occupational and non-occupational exposures. The more recent studies are summarised below.

- In a study among 853 patch-tested hard metal workers in Sweden, 39 (4.6%; 9 males and 30 females) were found to have a confirmed allergic reaction to 1% cobalt dichloride. (Nordberg *et al*, 2015).
- A recent study has found a positive and significant association between cobalt allergy and a history of dermatitis caused by non-occupational exposure to leather articles[7] showing cases of allergic cobalt dermatitis caused by consumer leather exposure (Bregnbak *et al,* 2017).
- A case of cobalt allergy on the skin contact with the prosthetic leg of a 30-year-old female patient was reported. The patient developed maculopapular and vesicular lesions on her contact region of residual limb to prosthetic leg. She underwent standard patch testing, which resulted in a strong positive reaction to cobalt dichloride (Arslan *et al,* 2015).
- Systemic contact dermatitis was caused by cobalt dichloride and palladium in a 26-year-old woman with allergic type I reactions, non-steroidal anti-inflammatory drug hypersensitivity and autoimmune thyroiditis (Panaszek *et al,* 2017).

Overall, the results from epidemiological and experimental studies show that the cobalt salts are skin and respiratory sensitisers. Evidence of occupational asthma has been found among workers exposed to cobalt and cobalt compounds.

On the other hand, information provided by three member states (Ireland, Finland and Slovakia) as part of the stakeholder consultation suggests an incidence of 1 to 3 cases of skin diseases and 0 to 1 asthma cases per year related to exposure to cobalt compounds, depending on the Member State. The data are presented in Table B.4.2.A and B.4.2.B below.

Table B.4.2.A. Number of cases of occupational skin diseases related to cobalt exposure

Member state	Substance	Period	No of cases	No of cases/year
Ireland	Cobalt compounds	2005-2017	30[a]	2.3
Finland[a]	Cobalt compounds	2014	3	3
Slovakia	Cobalt compounds	2017	1	1

[a] 30% cases in the construction industry, 17% cases in the manufacturing industry, 13% in social and health care sector, rest others

Table B.4.2.B. Number of cases of asthma related to cobalt exposure

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[7] Cobalt dichloride is used in the processing of leather articles (Bregnbak *et al*, 2017).

Member State	Substance	Period	No of cases	No of cases/year
Ireland	Cobalt compounds	2005-20017	1	0.08
Finland[a]	Cobalt compounds	2014	1	1
Slovakia	Cobalt compounds	2017	0	0

As shown above, the information provided does not identify the specific cobalt compounds to which exposure takes place. Although Finland submitted information on the number of cases of occupational skin diseases and asthma cases corresponding to the period 2007 to 2013, the data are related to exposure to cobalt and nickel compounds and therefore have not been included here.

All in all, the available information is too scarce to draw any firm conclusion on the prevalence of occupational skin diseases and asthma related to cobalt exposure in these member states or in the EU (approximately 3% of the population of the EU live in Ireland, Finland and Slovakia). Moreover, there is no specific information on the number of cases that may result as a consequence of exposure to the five cobalt salts within the scope of the restriction dossier.

The number of sensitisation cases reported by the Cobalt REACH Consortium in the public consultation seems to follow the same pattern. According to the information provided, the number of asthma cases reported in the last 10 years by the companies participating in a survey is zero while the number of skin sensitisation cases has been reported as less than 0.5 cases per year. The number of cases reported result from exposure to cobalt and cobalt compounds and cannot be related to the specific cobalt compounds covered by the restriction proposal.

In general terms the Dossier Submitter considers that the information available does not allow for the quantification of the incidence of sensitisation cases at the EU level.

B.4.3. Genotoxicity

B.4.3.1. *In vitro* data

From the IARC (2006) evaluation on the water soluble cobalt salts, it can be seen that generally there was a lack of mutagenic activity in bacteria, although isolated positive finds occurred and a comutagenic potential was noted in connection with co-exposure to known mutagens e.g. benzo(a) pyrene and napthtylamine.

In *Saccharomyces cerevisiae* gene conversion and petite ρ-mutation in mitochondrial DNA was seen, but no other types of mutation occurred.

IARC (2006) noted several positive results in mammalian cells cultured *in vitro* with respect to induction of DNA–protein cross-linkage, DNA strand breakage and sister chromatid exchange in most of the studies.

Further, cobalt dichloride induced mutations at the Hprt locus in Chinese hamster V79 cells, but not at the 8AG and the Gpt loci. At the same Gpt locus in a transgenic Chinese hamster V79 G12 cell line, lower concentrations of cobalt dichloride did induce gene mutations. In a single study, at the Tk locus in mouse lymphoma L5178Y cells, the results were negative. Also, cell transformation of Syrian hamster embryo cells was found to be induced by the cobalt salts (IARC, 2006).

In cultured human cells *in vitro*, positive results were noted for inhibition of protein-DNA binding activities and inhibition of p53 binding to DNA and for induction of gene expression (in Cap43 in human lung cells), induction of DNA strand breakage and sister chromatid exchange. In cultured human lymphocytes, induction of aneuploidy was noted (IARC, 2006).

When looking through the different expert evaluations, there are no substantial differences in the interpretation of the *in vitro* mutagenicity data, and it is overall acknowledged that cobalt metal particles and soluble cobalt salts have the capacity to cause DNA damage and chromosomal damage in mammalian cells *in vitro*.

It should, however, be noted that the negative results in bacteria may be due to the test conditions of the assays performed. The difficulty of detecting mutations due to cobalt and other metals and their salts in bacteria was shown by Pagano and Zeiger (1992) to be due to interaction with test media (precipitation in the PO_4-buffer, which is used as standard in the Ames test). If HEPES buffer or water was used instead, cobalt dichloride was much more potent in inducing gene mutations. A clear concentration response effect was observed from 12.5 to 800 µM and a more than threefold increase in revertants was observed already at 50 µM cobalt dichloride.

B.4.3.2. *In vivo* data

Rather limited *in vivo* genotoxicity data are available on the cobalt salts.

An overview of the experimental animal *in vivo* genotoxicity test results is shown below in Table 9.

Table 9: *In vivo* genotoxicity data on the cobalt salts. (Compiled from IARC, 2006; MAK, 2007; ECHC, 2011; OECD, 2014a; Kirkland *et al*, 2015) (ECHA Project SR 23, Larsen *et al,* 2015)

Substance and reference	**Assay**	**Exposure**	**Result**
	Intraperitoneal exposure		
Cobalt dichloride, Farah (1983)	Aneuploidy, male hamsters: - bone marrow - germ cells	400 mg/kg bw i.p. dosed over 9 days	Positive
Cobalt dichloride, Suzuki *et al* (1993)	Micronuclei, mice -bone marrow	25-90 mg/kg bw i.p.	Positive dose related
Cobalt dichloride, Rasgele *et al* (2013)	Micronuclei, Mice -bone marrow	11.2, 22.5, 45 mg/kg bw i.p.	Positive
Cobalt(di)acetate Kasprzak *et al* (1994)	Oxidative DNA base damage, rats - kidney, liver, lung	50 µM/kg bw i.p. (~2.9 mg Co/ kg bw)	Positive

Substance and reference	**Assay**	**Exposure**	**Result**
Oral exposure			
Cobalt dichloride, Palit *et al* (1991)	Chromosome abberation, mice -bone marrow	0, 20, 40, 80 mg/kg bw oral	Positive at all exposure levels and dose-related
Cobalt dichloride, Gudi (1998)	Chromosome abberation, rats -bone marrow	50,200,600 mg/kg bw oral	Negative
Cobalt sulphate Legault (2009)	Chromosome abberation, rats – bone marrow	80, 160, 320 mg/kg/d single dose oral, and during 5 days oral	Negative
Cobalt dichloride, Kirkland *et al* (2015)	Chromosome abberation, rats – sperm cells	0, 3, 10, 30 mg/kg bw/d oral during 28 days	Negative, no signs of toxicity noted apart from a small reduction in body weight
Inhalation exposure			
Cobalt sulphate, heptahydrate NTP (1998)	K-*ras* mutation, mice -lung neoplasms	0, 0.3, 1, 3 mg/m^3 inhalation 2 years	Positive

Intraperitoneal exposure

IARC (2006) highlighted three studies using i.p. administration. In these studies, cobalt dichloride induced aneuploidy (pseudodiploidy and hyperploidy) in bone marrow and testes of Syrian hamsters (Farah, 1983) and micronuclei in bone marrow in male BALB/c mice (Suzuki *et al*, 1993). Cobalt di(acetate) was shown to induce DNA base damage in female and male Fischer 344/NCr rats (Kasprzak *et al*, 1994).

Overall, the data indicate that the water cobalt salts are genotoxic in vivo in connection with i.p. administration (Farah, 1983; Suzuki *et al,* 1993; Rasgale *et al,* 2013; Kasprzak *et al,* 1994). Although these studies were acknowledged by the other expert assessments, the relevance of the studies by Farah (1983), Suzuki *et al* (1993) and Rasgale *et al* (2013) were questioned by OECD (2014) and Kirkland *et al* (2015) as the exposure route was not considered relevant for human exposure. Furthermore, shortcomings of the studies were argued (i.e. poor reporting, too high dose level used) and the increase in micronuclei found by Rasgele *et al* (2013) and Suzuki *et al* (1993) was suggested to be a follow from increased erythropoiesis. Although, different interpretations apply for these studies the data cannot be dismissed or neglected as indications for a genotoxic potential of water soluble cobalt salts *in vivo*. (ECHA Project SR 23, Larsen *et al,* 2015).

Also, i.p. micronucleus test data cannot be said to be irrelevant for the assessment of mutagenicity when it comes to a soluble in vitro genotoxic substance that is a potential lung carcinogen. When assessing i.p. micronucleus test data, there are two different issues:

(i) testing for inherent potential to be mutagenic in whole animals, the hazards of concern being anything in any tissue that could be caused by chemically-induced mutagenic lesions in DNA; and

(ii) testing specifically for the ability of a chemical to produce heritable mutations in the germ cells.

The *in vivo* micronucleus test (or a comparable chromosome aberration test) has been the key study to investigate substances that have been found to be genotoxic in *in vitro* systems. For all types of chemicals, the i.p. route has been considered valid internationally for this test since the early 1990es. Its use was routine in new substance dossiers, for example. The OECD test guideline No. 474, does not exclude the use of the i.p. exposure route, if justified, and such a justification could be that the target cells are to be regarded as a surrogate for any tissue in the body. In contrast, in tests such as comet, UDS and transgenic mice gene mutations, the targets are in specific tissues and the i.p. route may not be justified (ECHA Project SR 23, Larsen *et a,l* 2015).

Oral exposure

Palit *et al* (1991) dosed groups of five male Swiss albino mice orally with cobalt dichloride at 0, 20, 40 and 80 mg/kg, the top dose being 10 % of a lethal dose. Bone marrow preparations were made 6, 12, 18 and 24 hr later. Fifty metaphases were scored from each animal per sampling time. For all sample periods, a significant dose-related trend was observed for chromosome aberrations compared to the control group. The authors concluded that the chromosome damage was directly related to the exposure concentration of cobalt dichloride and also to the increased period after administration.

This study was referred to and cited in several of the expert assessments, e.g. WHO/CICAD (2006), MAK (2007), EFSA (2009) (but not IARC 2006). In the OECD (2014) assessment, the validity of the study was questioned as the clear dose-response and time-response relationship found in the study was considered to be a very unusual finding and thus the study was found to be of limited relevance.

Instead, OECD (2014) focussed on two unpublished oral studies by Gudi (1998) and Legault (2009), which are studies not covered by the other expert group assessments:

Gudi (1998) studied bone marrow chromosome aberration in groups of male and female Sprague-Dawley rats at oral dose levels of 50, 200 and 600 mg/kg of cobalt dichloride hexahydrate. The substance was dissolved in water and administered once by oral gavage. Some animals died at the highest dose, and also at the next lower dose (200 mg/kg), and so both of these dose levels were higher than the MTD. Clinical signs, including lethargy and piloerection, indicated systemic exposure. Animals were administered colchicine 2-4 hrs before sacrifice in order to arrest dividing cells of the bone marrow in metaphase. Most animals were sacrificed 18 hrs after dosing, while others 42 hrs after dosing (not clearly indicated). Bone marrow was aspirated from 1 femur per animal. Where possible, 100 cells per animal were analysed microscopically for presence of chromosome aberrations. There were some reductions in mitotic index in the bone marrow preparations of treated animals (up to 34% reduction compared to control), which may be taken as indicative of bone marrow toxicity. In addition, severe reductions in the percentage of polychromatic erythrocytes gave clear indications of bone marrow toxicity. Frequencies of chromosomal aberrations in treated groups were low and similar to control, and there were no significant increases. Thus, cobalt dichloride hexahydrate did not induce chromosome aberrations in bone marrow of rats at lethal doses that induced bone marrow toxicity (OECD, 2014).

Legault (2009) studied bone marrow chromosomal aberration in rats following single oral administration to cobalt sulphate at dose levels of 80, 160 and 320 mg/kg cobalt sulphate (two rats per dose group). Further, in a multi-dose study, rats (5 rats per group) were exposed orally to 100, 300 and 1000 mg/kg cobalt sulphate daily for 5 days; however, only the low-dose animals survived the five days of dosing. Fifteen hours after the last dosing, the animals were given 4 µg/kg colchicine to accumulate bone marrow cells in metaphase, and one hour later they were sacrificed and bone marrow smears were made and stained. Chromosome aberrations were scored from 100 cells/animal. Chromosome aberrations were within normal ranges at 160 and 320 mg/kg whereas chromosome aberration frequencies in the range of 5 % were noted at the dose-level of 80 mg/kg. These were considered outside historical controls but were not different from the vehicle control values without colchicine (OECD, 2014).

Very recently, Kirkland *et al* (2015) further described the data from this study as the study also covered results from repeated oral exposure of five male and five female rats to 100 mg/kg/d, 300 mg/kg/d and 1000 mg/kg/d (these data were not clearly reported in OECD (2014)). Due to high mortality at the two highest dose levels, results only became available from the low dose group (after five days of exposure) and from the high dose group (after two days of exposure). The frequency of chromosome aberration in the control group was very low (0.2 %) so although a level of 1.2 % was found in the high dose group, this was not considered an effect attributed to the exposure.

In addition to this, Kirkland *et al* (2015) reported data from a study where chromosome aberrations in sperm cells were studied after 28 days of oral exposure of rats to 0, 3, 10 and 30 mg/kg/d of cobalt chloride. Higher dose levels of 100 mg/kg/d and 300 mg/kg/d were not tolerated by the animals. The frequencies of chromosome aberrations were determined from 200 metaphases per animal. No signs of toxicity were noted in the study apart from a small reduction in body weight. At none of the dose levels, increased frequencies of chromosome aberrations or of polyploidy were observed. Data on mitotic index did not indicate toxicity towards the bone marrow cells.

It is acknowledged that the data, as tabulated in the original reference by Palit *et al* (1998), can be considered rather unusual as clear stepwise dose-responses can be seen for chromosome aberrations in relation to the three dose levels used (in the interval from 20-80 mg/kg), and a clear time-response relationship was seen for the four timing intervals for the sampling of bone marrow cells. Therefore, it may be difficult to make any firm conclusion based on this study that indicates a clear positive response.

In opposition to this, the study by Gudi (1998) did not find induction of chromosome aberrations in the bone marrow in rats exposed to cobalt dichloride at higher and cytotoxic doses. The study has not been published and has therefore not undergone a peer-review.

The study by Legault (2009) is less informative, as the increase in chromosome aberrations at the lowest dose level after single exposure compared to the higher dose levels is difficult to interpret. In addition, the findings in relation to repeated exposure were considered negative, but only data from one dose level were obtained. The study has not been peer-reviewed.

Thus, to some extent weight of evidence suggests a lack of genotoxic effects after oral exposure. However, no firm conclusion can be made based on these data. Although some doubt pertain to the Palit *et al* (1998) study, differences in species sensitivity towards the genotoxicity in bone marrow of the cobalt (II) ion cannot be ruled out.

Inhalation exposure

In relation to inhalation exposure, NTP (1998) examined tissues from lung neoplasms in mice obtained from the 2-year inhalational carcinogenicity study for genetic alterations in the K-ras gene. A dose response relationship in the frequency of K-ras mutations was observed in cobalt sulphate heptahydrate-induced lung neoplasms: 14 %, 38 %, and 45 % at the dose levels of 0.3, 1.0, and 3.0 mg/m^3 doses, respectively. There were generally no differences in the mutation frequency or spectra between benign and malignant lung neoplasms. NTP (1998) noted that the higher number of K-ras mutations (G to T transversions at codon 12) is supportive evidence that cobalt sulphate heptahydrate may indirectly damage DNA by oxidative stress. According to NTP (1998), the observation of similar frequencies and spectra of mutations in cobalt sulphate heptahydrate-induced alveolar/bronchiolar adenomas and carcinomas is consistent with other studies showing that K-ras activation occurs as an early and initiating event. If mutations in the K-ras gene occurred later in the carcinogenic process, an increased frequency of K-ras mutations would have been expected in the carcinomas.

Human data

OECD (2014) and IARC (2006) referred to a study by De Boeck *et al* (2000) in which comet assays and micronuclei detection were performed on lymphocytes from 35 workers exposed to cobalt and inorganic cobalt salts (average exposure level estimated to be 0.020 mg Co/m^3 based on 5 weeks measurement of urinary concentration of 0.020 mg Co/g creatinine). Micronuclei were scored both as binucleates (MNCB) and as mononucleates (MNMC) to discriminate between micronuclei accumulated during chronic exposure *in vivo* (mononucleates) and additional micronuclei expressed during the culture period *in vitro* (binucleates). Also biomarkers of DNA damage: 8-hydroxy-deoxyguanosine (8-OHdG) in urine, DNA single-strand breaks and formamido-pyrimidine DNA glycosylase (FPG)-sensitive sites with the alkaline Comet assay in mononuclear leukocytes were determined. No significant increase in genotoxic effects was detected in workers exposed to cobalt-containing dust compared with controls. No difference in any genotoxicity biomarker was found between workers exposed to cobalt and to hard-metal dusts (a further group included). It was found that smoking status affected the levels of micronucleated binucleates (MNCB) in lymphocytes; however, the exposure to cobalt was not found to induce an increased frequency as compared to a control group.

The Swedish Work and Health report (SWH 2005a) referred to a study by Hengstler *et al* (2003) that studied DNA-damage in mononuclear blood cells from 78 workers subject to a combined exposure to cobalt, lead and cadmium. A strong correlation between DNA single strand breaks and cobalt exposure was found among workers exposed to mean levels in the range of 4-10 µg Co/m^3 (species not indicated). An inhibition of repair activity of DNA adducts (8-oxoguanine) in blood from these workers was also reported (referred to as unpublished data). The authors concluded that cobalt was the strongest determinant for DNA-damage, but that interactions with cadmium and/or lead seemed likely.

MAK (2007) referred to a study by Oesch *et al* (1999), in which increased numbers of DNA single strand breaks and reduced repair capacity for oxidative DNA damage in lymphocytes were found in a subgroup of 11 workers from a groups of 78 metal workers, who were exposed to > 4 µg/m^3 of cobalt (species not indicated) at the work site. Although the workers were exposed to considerably higher cadmium levels as well, statistical analysis revealed that the cobalt exposure had the dominant impact on the occurrence of strand breaks.

B.4.3.3 Conclusions on genotoxicity

Only very limited and non-conclusive human data are available with respect to the assessment of genotoxic effects from cobalt/ cobalt salt exposure.

Most consistently the cobalt (II) ion is considered genotoxic *in vitro* due to the induction of chromosome damage in mammalian cells.

In addition:

- Several i.p. studies on water soluble cobalt salts have been positive for genotoxic effects after systemic uptake.
- Oral studies are non-conclusive i.e. no clear evidence on systemic genotoxicity after oral exposure.
- There may be local genotoxic effects, but these have not been really studied in appropriate studies (e.g. by *in vivo* comet assay in respiratory epithelial cells). NTP results on k-*ras* mutations in lung tumours suggest oxidative damage in lung tissue. In addition, i.p. data indicate oxidative damage on DNA.

Based on this it is concluded that genotoxicity as a mode of action behind lung tumours cannot to be ruled out.

B.4.4. Carcinogenicity

B.4.4.1. Experimental animal data

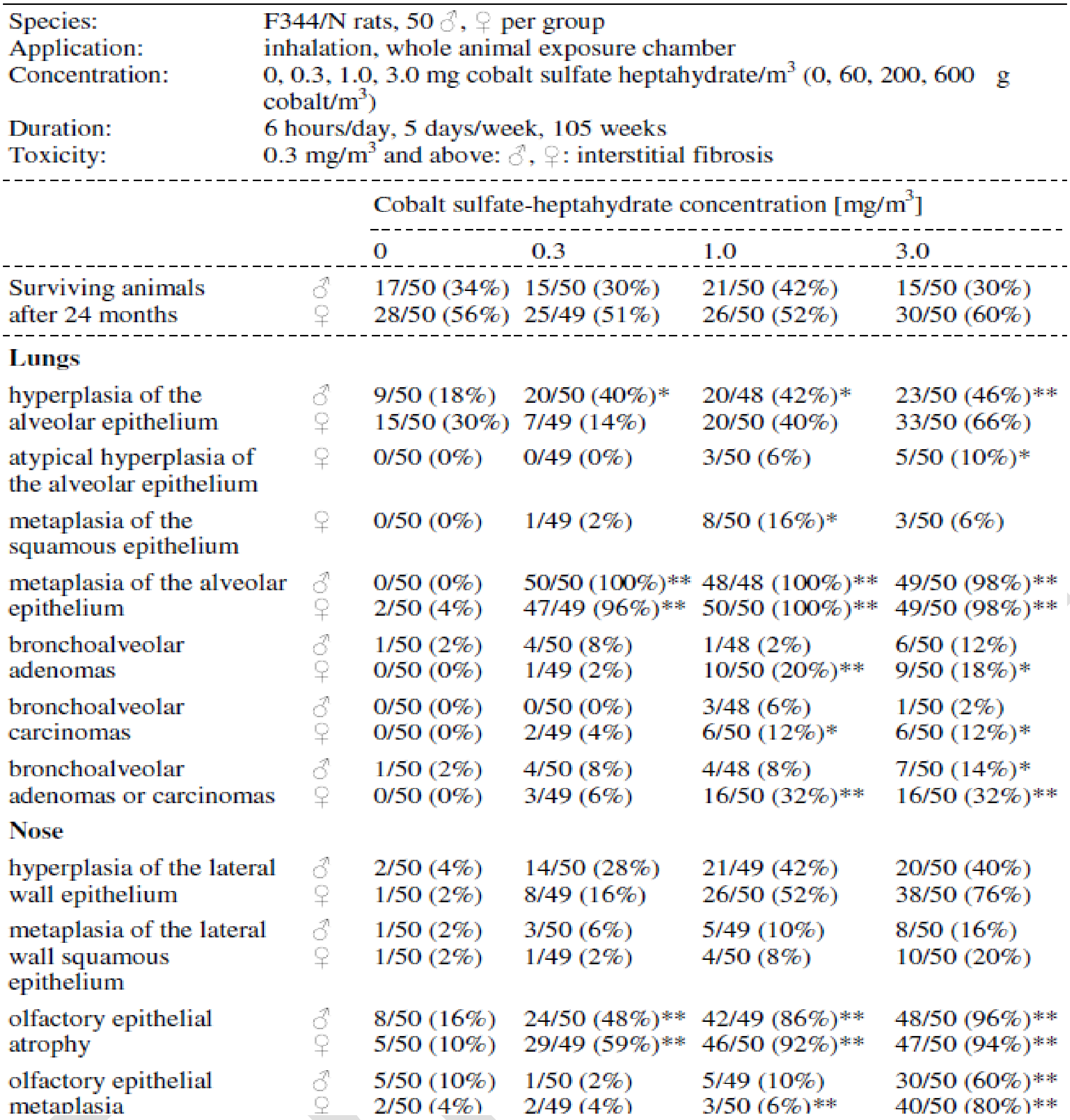
Significant dose-related increases were seen for alveolar/bronchiolar neoplasms in all dose groups in male and female mice and rats exposed to cobalt metal by inhalation. Tumours were also induced at sites distant from the lung in rats, including tumours of the pancreas in males and of the hematopoietic system (mononuclear-cell leukaemia) in females, indicating a systemic effect. Increased incidence of neoplasms in the kidney in male rats and pancreas in female rats may have been related to cobalt metal inhalation. Exposure to cobalt metal also induced adrenal gland tumours (benign and malignant pheochromocytomas) in male and female rats which could be caused by direct or indirect mechanisms (NTP, 2014).

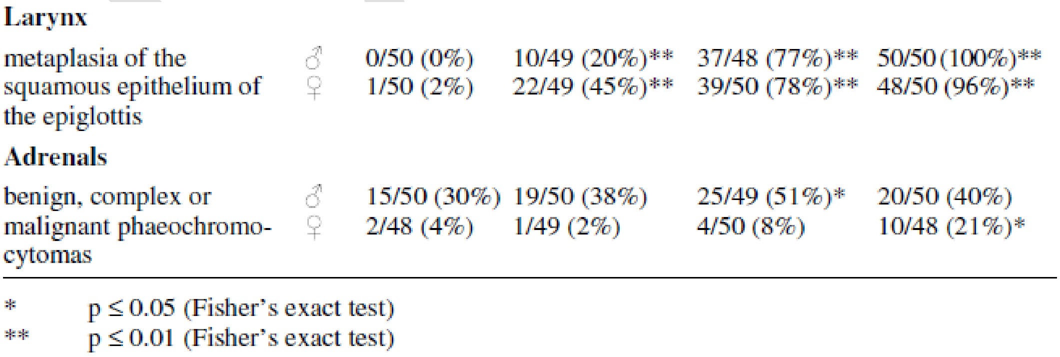
Two 2-year carcinogenicity studies with inhalational exposure to cobalt sulphate in rats and mice are available (NTP, 1998; Bucher, 1999). In these studies, increased incidences of alveolar/bronchiolar neoplasms in both sexes of both species at concentrations ≥ 0.3 mg/m³ cobalt sulphate heptahydrate (equivalent to ≥ 0.067 mg Co/m³) were seen (see tables x and x below with detailed information). No NOAEC for formation of lung tumours could be derived from these studies.

Based on the findings from these studies, OECD (2014) calculated benchmark doses (BMD) using the US EPA BMD software (Version 2.0) with the Gamma Model (Version 2.13). The numbers of alveolar/bronchiolar adenoma or carcinoma in the lungs of rats and mice were selected as benchmark response. The 95 % lower confidence limit of the BMD for a treatment-related increase in response of 10 % was calculated (BMDL10). The lowest BMDL10 value of 0.414 mg/m³ cobalt sulphate heptahydrate was found for female rat tumours.

It should be noted that in the NTP (1998) study, increased incidences of liver hemangiosarcomas occurred in male mice, which may indicate concern for carcinogenic effects after systemic uptake as well (which then also could be relevant for systemic uptake from other routes of exposure). However, the male mice were infected with *Heliobacter Hepaticus* and in earlier NTP studies, infections caused by *Heliobacter Hepaticus* had led to increased incidences of hemangiosarcoma in the livers of the mice. Therefore, this finding could not be associated to the cobalt sulphate exposure (NTP, 1998; Bucher, 1999).

Table 10: Results of the NTP study on the carcinogenicity of cobalt sulphate in rats from the NTP (1998) study (Table from MAK, 2007)





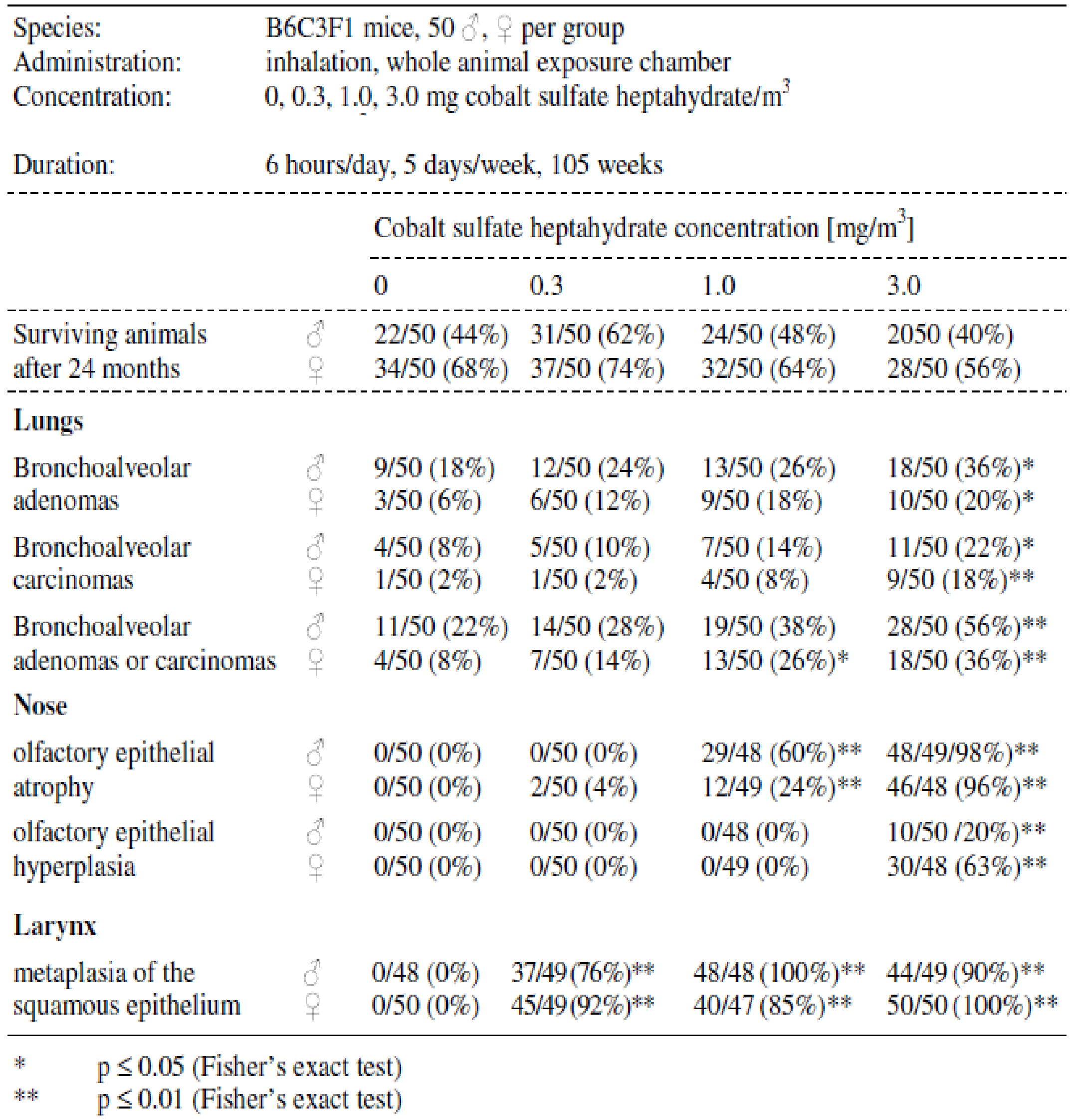
Species:	F344/N rats, 50 ♂, ♀ per group
Application:	inhalation, whole animal exposure chamber
Concentration:	0, 0.3, 1.0, 3.0 mg cobalt sulfate heptahydrate/m^3 (0, 60, 200, 600 g cobalt/m^3)
Duration:	6 hours/day, 5 days/week, 105 weeks
Toxicity:	0.3 mg/m^3 and above: ♂, ♀: interstitial fibrosis

		Cobalt sulfate-heptahydrate concentration [mg/m^3]			
		0	0.3	1.0	3.0
Surviving animals after 24 months	♂ ♀	17/50 (34%) 28/50 (56%)	15/50 (30%) 25/49 (51%)	21/50 (42%) 26/50 (52%)	15/50 (30%) 30/50 (60%)
Lungs					
hyperplasia of the alveolar epithelium	♂ ♀	9/50 (18%) 15/50 (30%)	20/50 (40%)* 7/49 (14%)	20/48 (42%)* 20/50 (40%)	23/50 (46%)** 33/50 (66%)
atypical hyperplasia of the alveolar epithelium	♀	0/50 (0%)	0/49 (0%)	3/50 (6%)	5/50 (10%)*
metaplasia of the squamous epithelium	♀	0/50 (0%)	1/49 (2%)	8/50 (16%)*	3/50 (6%)
metaplasia of the alveolar epithelium	♂ ♀	0/50 (0%) 2/50 (4%)	50/50 (100%)** 47/49 (96%)**	48/48 (100%)** 50/50 (100%)**	49/50 (98%)** 49/50 (98%)**
bronchoalveolar adenomas	♂ ♀	1/50 (2%) 0/50 (0%)	4/50 (8%) 1/49 (2%)	1/48 (2%) 10/50 (20%)**	6/50 (12%) 9/50 (18%)*
bronchoalveolar carcinomas	♂ ♀	0/50 (0%) 0/50 (0%)	0/50 (0%) 2/49 (4%)	3/48 (6%) 6/50 (12%)*	1/50 (2%) 6/50 (12%)*
bronchoalveolar adenomas or carcinomas	♂ ♀	1/50 (2%) 0/50 (0%)	4/50 (8%) 3/49 (6%)	4/48 (8%) 16/50 (32%)**	7/50 (14%)* 16/50 (32%)**
Nose					
hyperplasia of the lateral wall epithelium	♂ ♀	2/50 (4%) 1/50 (2%)	14/50 (28%) 8/49 (16%)	21/49 (42%) 26/50 (52%)	20/50 (40%) 38/50 (76%)
metaplasia of the lateral wall squamous epithelium	♂ ♀	1/50 (2%) 1/50 (2%)	3/50 (6%) 1/49 (2%)	5/49 (10%) 4/50 (8%)	8/50 (16%) 10/50 (20%)
olfactory epithelial atrophy	♂ ♀	8/50 (16%) 5/50 (10%)	24/50 (48%)** 29/49 (59%)**	42/49 (86%)** 46/50 (92%)**	48/50 (96%)** 47/50 (94%)**
olfactory epithelial metaplasia	♂ ♀	5/50 (10%) 2/50 (4%)	1/50 (2%) 2/49 (4%)	5/49 (10%) 3/50 (6%)**	30/50 (60%)** 40/50 (80%)**
Larynx					
metaplasia of the squamous epithelium of the epiglottis	♂ ♀	0/50 (0%) 1/50 (2%)	10/49 (20%)** 22/49 (45%)**	37/48 (77%)** 39/50 (78%)**	50/50(100%)** 48/50 (96%)**
Adrenals					
benign, complex or malignant phaeochromocytomas	♂ ♀	15/50 (30%) 2/48 (4%)	19/50 (38%) 1/49 (2%)	25/49 (51%)* 4/50 (8%)	20/50 (40%) 10/48 (21%)*

* $p \leq 0.05$ (Fisher's exact test)

** $p \leq 0.01$ (Fisher's exact test)

Table 11: Results of the NTP study on the carcinogenicity of cobalt sulphate in mice from the NTP (1998) study (Table from MAK, 2007)



Species: B6C3F1 mice, 50 ♂, ♀ per group
Administration: inhalation, whole animal exposure chamber
Concentration: 0, 0.3, 1.0, 3.0 mg cobalt sulfate heptahydrate/m³

Duration: 6 hours/day, 5 days/week, 105 weeks

		Cobalt sulfate heptahydrate concentration [mg/m³]			
		0	0.3	1.0	3.0
Surviving animals after 24 months	♂	22/50 (44%)	31/50 (62%)	24/50 (48%)	2050 (40%)
	♀	34/50 (68%)	37/50 (74%)	32/50 (64%)	28/50 (56%)
Lungs					
Bronchoalveolar adenomas	♂	9/50 (18%)	12/50 (24%)	13/50 (26%)	18/50 (36%)*
	♀	3/50 (6%)	6/50 (12%)	9/50 (18%)	10/50 (20%)*
Bronchoalveolar carcinomas	♂	4/50 (8%)	5/50 (10%)	7/50 (14%)	11/50 (22%)*
	♀	1/50 (2%)	1/50 (2%)	4/50 (8%)	9/50 (18%)**
Bronchoalveolar adenomas or carcinomas	♂	11/50 (22%)	14/50 (28%)	19/50 (38%)	28/50 (56%)**
	♀	4/50 (8%)	7/50 (14%)	13/50 (26%)*	18/50 (36%)**
Nose					
olfactory epithelial atrophy	♂	0/50 (0%)	0/50 (0%)	29/48 (60%)**	48/49/98%)**
	♀	0/50 (0%)	2/50 (4%)	12/49 (24%)**	46/48 (96%)**
olfactory epithelial hyperplasia	♂	0/50 (0%)	0/50 (0%)	0/48 (0%)	10/50 /20%)**
	♀	0/50 (0%)	0/50 (0%)	0/49 (0%)	30/48 (63%)**
Larynx					
metaplasia of the squamous epithelium	♂	0/48 (0%)	37/49(76%)**	48/48 (100%)**	44/49 (90%)**
	♀	0/50 (0%)	45/49(92%)**	40/47 (85%)**	50/50 (100%)**

* p ≤ 0.05 (Fisher's exact test)
** p ≤ 0.01 (Fisher's exact test)

Furthermore, adrenal pheochromocytomas were increased in female rats, and to some extent in male rats (NTP, 1998; Buchner 1999). Adrenal gland neoplasms can develop because of damage to the lungs that causes systemic hypoxemia leading to chronic inflammation and subsequent neoplasm developments (NTP, 2014). It is possible that the adrenal glands neoplasms observed may not be directly caused by systemic exposure to cobalt but could be a secondary response to lung damage.

Based on the experimental studies of inhalation exposure to cobalt sulphate, it has been previously considered that the local induction of alveolar/bronchiolar tumours in the lungs is the only carcinogenic relevant response from inhalation exposure to the cobalt salts (ECHA Project SR 23, Larsen *et al,* 2015). However, experimental findings in cobalt metal studies support the evidence of systemic exposure of rats and mice to cobalt. Cobalt concentrations and burdens increased with increasing exposure concentrations in all studies in all tissues examined. In addition neoplasms were observed at several organ sites (pancreas, hematopoietic system and kidney) distal to the route of administration. Therefore the induction of systemic carcinogenicity effects via the inhalation route is also considered relevant. Potential local and systemic effects via other routes of exposure (dermal, oral) cannot be discarded (ECHA, 2017b).

B.4.4.2.Human data

Very limited human data are available with regard to the carcinogenicity of the cobalt salts. (ECHA, 2016). Thus, only two epidemiological studies concerning occupational exposure to cobalt salts have been identified by OECD (2014) as well as by IARC (2006). These two studies are briefly discussed below.

Mur *et al* (1987) studied the mortality in a cohort of 1 143 workers at an electrochemical plant in France that produced cobalt, cobalt oxides, cobalt salts and sodium. The cohort included all men who had worked one year or more between 1950 and 1980 and was split in several subgroups related to their tasks in the production. However, the exposure levels of cobalt were not reported. Among cobalt production workers, there was a relative increase in deaths from cancers of the trachea, lungs and bronchus (SMR 4.66; 95 % CI 1.46-10.64 based on four cases). No corrections for cigarette smoking were possible. The relationship between cobalt production and lung cancer mortality seemed to be supported by a case-control analysis nested in the cohort study. Among cases of deaths from lung cancer, there were 44 % of the workers who had ever been employed at the cobalt production (all for more than 10 years); there were only 17 % among the controls. However, the difference was not statistically significant. The interpretation of this study should be done with caution due to the low number of cases and because the role of smoking and of simultaneous exposure to arsenic and nickel could not be taken into account.

Moulin *et al* (1993) did a follow-up study of the same population, extending the observation period from 1980 to 1988. The total cohort comprised 1 148 subjects. The SMR for all causes of death was 0.85 (95 % CI 0.76-0.95) for the whole cohort, and 0.95 (95 % CI 0.78-1.26) for the sub-cohort of workers born in France. With regard to lung cancer mortality among cobalt production workers, the SMRs were 0.85 (95 % CI 0.18-2.50, 3 cases) for the whole cohort and 1.16 (95 % CI 0.24-3.40, 3 cases) for the sub-cohort. Any excess of mortality from diseases of the circulatory and of the respiratory systems did not appear among cobalt production workers. Maintenance workers, however, exhibited a non-significantly elevated SMR for lung cancer (1.80, 95 % CI 0.78-3.55), reaching statistical significance for duration of exposure and time since first exposure ≥ 30 years. This finding could not be clearly explained apart from the fact that asbestos exposure may have occurred. Again, it may be noted that the study is limited by the very small number of cases.

Epidemiology studies related to exposure to cobalt and tungsten carbide in the hardmetal[8] industry are also available. Lasfargues *et al* (1994) reported on the mortality of a cohort of 709 male workers in a French hardmetal[9] plant, using the national rates for French males for comparison. The overall mortality did not differ from expected, but there was a significant increase in mortality due to cancer of the trachea, bronchus, and lung (SMR=2.13, 95% CI=1.02–3.93). Smoking alone did not account for the lung cancer excesses, although the influence of smoking on the observed mortality could not be entirely ruled out (ATSDR, 2004).

According to NTP (2016), there is inadequate evidence from studies in humans to evaluate the association between exposure to cobalt and cobalt compounds that release cobalt ions *in vivo* and cancer. Although almost all the cohort studies assessed reported approximately a doubling of the risk of lung cancer from exposure to various cobalt compounds, NTP concluded it was unclear that the excess risks were due to exposure specifically to cobalt because of potential confounding from exposure to known lung carcinogens or other limitations. In addition, the studies were found to have limited sensitivity to detect a true risk because of

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[8] According to IARC (2006) , there is experimental evidence showing that the mixture of cobalt and tungsten carbide causes effects that are more severe than those observed with cobalt metal alone

small number of cases, crude exposure assessment, or concern about healthy worker related effects (NTP, 2016).

Several epidemiology studies have shown statistically significant increased cancer risk for lung (Lasfargues et al, 1994; Wild et al, 2000), trachea (Lasfargues et al, 1994), bronchus (Lasfargues et al, 1994), and tongue (Sauni et al, 2017) in workers occupationally exposed to cobalt in hardmetal production and in cobalt manufacturing. In spite of the positive associations between exposure to cobalt and occupational cancer risks found, the available studies present a number of limitations (small number of study subjects, limited information on exposures, confounding exposure to other carcinogens including smoking) that prevent to draw a definite conclusion on the excess cancer risk related to occupational exposure to cobalt. RAC (ECHA, 2017 b) in the context of the development of the opinion on the classification and labelling of cobalt metal concluded that the available epidemiological studies were not useful to conclude whether cobalt is carcinogenic in humans due to co-exposure to other carcinogens.

In their evaluation RAC considered two epidemiological studies recently published (Sauni *et al*, 2017; Marsh *et al*, 2017) not included in previous assessments. The Sauni study (Sauni *et al*, 2017) evaluated the cancer incidence among workers (995 males) employed in a Finnish cobalt plant for at least a year between 1968 and 2004. In this study, occupational exposure to cobalt was not associated with an increased overall cancer risk or lung cancer risk. The only cancer type with increased incidence was tongue cancer. However, because of the small size of the study, RAC concluded that the results must be interpreted with caution.

The second study is a large international occupational epidemiologic investigation of hard metal[10] workers (Marsh *et al*, 2017). The study combine five individual country cohorts from Austria, Germany, Sweden, UK and USA and altogether involved 32354 workers from three companies and 17 manufacturing sites. The authors concluded that at levels experienced by the workers examined there was no evidence that work in the participating hardmetal industry increased mortality risks from lung cancer or any other causes of death. Thus, this large study showed no consistent evidence of elevated lung cancer mortality risk among cobalt exposed hard metal workers. RAC (ECHA, 2017 b).

Based on the request of RAC, the Dossier Submitter has performed a more detailed assessment of the epidemiology study by Marsh et al, which is presented below.

Assessment of the pooled analysis of Marsh et al (2017)

Marsh *et al* (2017) conducted the so far largest epidemiological study related to cobalt exposure and mortality. By combining data from national cohorts they studied total and cause-specific mortality among 32 354 hardmetal production workers from 17 manufacturing sites in five countries (Austria, Germany, Sweden, UK, US). Special emphasis was on lung cancer risk in relation to exposure to Co, Ni and W. Mortality data was collected for 1952-2014. About 38% of the workers were born after 1960, 53% were hired after 1979 and 73% were men.

Based on quantitative job-exposure matrices, exposure estimates were generated for Co, Ni and W for the period of 1952-2014 (jobs held before 1952 were assigned 1952 exposures). The job-specific exposure data used covered the set of industrial hygiene measurements available for all the manufacturing sites involved (see Kennedy et al. 2017). Personal sampler data were preferred. Although there was variation as regards if total aerosol or inhalable particles had been measured, the available particle size distribution data indicated that any correction for that would have only a minimal effect and was therefore not applied. Respirable

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[10] Hard metal is an alloy of tungsten carbide and cobalt.

fraction estimates were not generated as there was limited availability of such measurement data and also lacking process/engineering data that would allow generating modelled estimates.

The exposure intensity to cobalt showed a median of 6 µg Co/m^3 and a ratio mean of 13 µg Co/m^3 (ratio mean calculated as sum of cumulative exposure divided by sum of duration of exposure across all workers with known work history). The exposure range was from 1 to 300 µg Co/m^3. Due to process improvements and tightening national occupational exposure limits, the cobalt exposures indicated a decline over time.

The risk analyses were focused on those cohort members who had worked at least 1 year in hardmetal production (22 506 persons, 544 845 person-years of follow-up). Risk estimates were calculated using both internal reference (relative risk (RR) compared to the lowest exposure category) and external reference (standardised mortality ratios (SMR) compared to regional rates).

Overall the lung cancer mortality was not statistically significantly increased among workers with at least 1 year of employment (SMR 1.10 (95% CI 0.97 – 1.23). Relative risks by exposure years, average intensity or cumulative exposure to either Co, Ni or W did not indicate a statistically significant exposure relationship between those exposures and lung cancer mortality. The results for Co by intensity and cumulative exposure are shown in Table B.4.4.2. These estimates are not adjusted for smoking or for Ni or W exposure. However separate analyses using the indirect adjustment method of Richardson (2010) and Richardson et al (2014) were performed to assess confounding by smoking but only at dichotomous level of exposure to Co (exposed/unexposed). The smoking unadjusted relative risk of 1.07 (95% CI 0.74 – 1.53) was reduced to 0.91 (95% CI 0.53 – 1.30) after adjustment. Assuming that adjustment for smoking would influence the dose-specific RRs of Table B.4.4.2 similarly, those risk estimates above 1 would be reduced towards 1.

Table B.4.4.2. Relative risk (RR) and standardized mortality ratio (SMR) of lung cancer by mean and cumulative exposure to Cobalt (pooled cohort, at least 1 year of employment)

Exposure		N of deaths	RR* (95% CI)		SMR (95% CI)
Mean intensity (µg Co/m^3)				P for trend	
	< 1.9	35	1.00 ref		1.04 (0.73 – 1.45)
	2.0 – 4.9	73	0.84 (0.56 – 1.27)	0.065	0.93 (0.73 – 1.16)
	5.0 – 10.9	95	1.22 (0.82 – 1.82)		1.30 (1.05 – 1.58)
	≥ 11.0 -	82	1.18 (0.79 – 1.77)		1.15 (0.92 – 1.43)
Cumulative (µg Co/m^3 -yrs)					
	< 9.1	29	1.00 ref		0.83 (0.56 – 1.19)
	9.1 – 39.3	74	1.31 (0.85 – 2.03)	0.302	1.15 (0.90 – 1.44)
	39.4 – 127	91	1.51 (0.99 – 2.31)		1.31 (1.06 – 1.61)
	≥ 128	91	1.31 (0.85 – 2.01)		1.03 (0.83 – 1.27)

* Adjusted for age, calendar time, gender and country

The two highest exposure intensity categories in Table B.4.4.2 represent exposures either slightly below or above 10 µg Co/m^3. For 10 µg Co/m^3 the dose-response derived from lung tumour incidence in animal data predicts an excess lifetime risk of lung cancer of 1 x 10^{-2} assuming an exposure duration of 40 years at work (see section B.4.5). The cumulative lung cancer incidence in the European population until the age of 75 years is 5.5 x 10^{-2} for men (i.e. 5.5%), 2.2 x 10^{-2} for women and 3.8 x 10^{-2} both sexes combined (IARC Globocan database), i.e. observing the excess lifetime risk of 1 x 10^{-2} above the background incidence in the general population would roughly correspond to a relative risk in the exposed population of 1.2 (= (1 + 5.5)/5.5) for men or 1.3 (= (1 + 3.8)/3.8) both sexes combined. While no clear correlation was observed between lung cancer mortality and exposures occurring in hardmetal production, it is to be noted that detecting or excluding with confidence such levels of relative risk in an epidemiological study is challenging. Actually, the smoking-unadjusted relative risks observed for lung cancer (albeit without statistical significance) for these groups around average intensity of 10 µg Co/m^3 (see Table B.4.4.2) are not clearly deviating from the order of magnitude of risk predicted by the animal data. As regards the third highest exposure category, the challenges would be even higher as the lifetime excess predicted for those exposure levels is of the order of 10^{-3}.

However, it is to be noted that the above comparisons are very rough and do not allow addressing some important aspects. Firstly, the hardmetal worker cohort was relatively young and the average exposure time is much shorter (and thus cumulative exposure lower) than the 40 years assumed in the animal data based calculation of risk per given exposure intensity. After exclusion of those with less than 1 year of employment, roughly one third had an exposure duration of 1-4 years, one third 5-19 and one third at least 20 years. The authors themselves conclude that the relatively young age distribution of the cohort would warrant continued mortality follow-up. Secondly, the dose response agreed by RAC (ECHA 2016) was derived for the cobalt salts and for the respirable fraction while the exposure estimates in the hardmetal worker cohort represent exposure to the inhalable fraction of cobalt metal[11]. Thirdly, the data indicate that the lung cancer risk estimates of Table B.4.4.2 might be too high as there was positive confounding by smoking. Finally, it is noteworthy that the RR calculations of Marsh *et al* (2017) were not using as a reference an entirely unexposed population, but those whose average exposure was below 2 µg Co/m^3. This means on one hand that very little can be concluded as regards risks at exposures below this limit and on the other hand, that the risks for the higher exposure categories could have been slightly higher if a truly unexposed reference population had been available (provided that the mode of action is non-thresholded). The unaccounted factors mentioned in this paragraph would have influenced the observed exposure-response relationships to different directions.

To conclude, the pooled analysis identified no clear relationship between the exposure to cobalt and mortality from lung cancer and the data indicate that adjustment for smoking might have further reduced the observed lung cancer risk estimates for specific cobalt exposure levels. However, due to the uncertainties described above, the Dossier Submitter considers that the data do not allow robustly, either identifying a threshold for cobalt exposure, or quantitatively modifying the dose-response derived from the animal data at levels of exposure experienced by the hardmetal workers followed. However, there seems not to be any indication that the risk estimates for humans would be higher than those predicted from the rat.

In general terms, the human data are considered too limited to draw any conclusions regarding the carcinogenicity of the cobalt salts.

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[11] According to NTP report (NTP,2016): “a comparison of the inhalation studies conducted by NTP of cobalt metal and cobalt sulphate suggests that cobalt metal was more toxic and carcinogenic at a similar cobalt concentration as evidenced by the incidence and spectrum of lung neoplasms and the extent of systemic lesions”.

B.4.4.3. Mode of action

Although the underlying mechanisms for the potential genotoxic and carcinogenic effects of the cobalt salts have not been fully elucidated, the current evidence support the following primary modes of action as described by Beyersmann and Hartwig (2008):

Induction of ROS and oxidative stress

The cobalt (II) ions are able to induce the formation of reactive oxygen species (ROS) both *in vitro* and *in vivo*, and further they catalyse the generation of hydroxyl radicals from hydrogen peroxide in a Fenton type reaction. The mechanism was supported by an i.p. study by Kasprzak *et al* (1994) in which cobalt (II) resulted in the formation of oxidative DNA damage in kidneys, liver and lungs. In addition, the analysis of mutations in tumour tissues in a carcinogenicity study with cobalt sulphate in mice (NTP, 1998) revealed that five of nine mutations were G-T transversions in codon 12 of the K-*ras* oncogene, which might be due to oxidative DNA damage.

Inhibition of DNA repair

Data have shown that the genotoxic effects of other mutagenic agents were enhanced by soluble cobalt salts as well as by cobalt metal dust. Further, cobalt (II) inhibited the nucleotide excision repair of DNA damage caused by UV-C radiation in human fibro-blasts. Both the incision and polymerisation steps were inhibited. In particular, cobalt inhibited the Xeroderma pigmentosum group A (XPA) protein, a zinc finger protein involved in nucleotide excision repair where cobalt(II) substituted the zinc ion.

These *in vitro* findings are coherent with the co-carcinogenic effect found *in vivo*, where cobalt (II) oxide enhanced the carcinogenicity of benzo[a]pyrene (Steinhoff and Mohr, 1991) using intratracheally administration of the substances.

Upregulation of hypoxia-inducible factor HIF-1α

Data have shown that cobalt (II) ions induce upregulation of hypoxia-inducible factor HIF-1α. Such upregulation is known to induce hypoxia and promote tumour growth.

There is a general consensus among the expert group assessments that especially ROS generation and impaired DNA repair are relevant modes of action for the genotoxic effects of the cobalt (II) ion. However, to which extent the available knowledge suffice to conclude on a threshold or non-threshold mechanism in a REACH context is less clear.

Overall, sufficient information is not available to make firm conclusions to whether the cobalt salts can be considered threshold or non-threshold carcinogens. This is reflected in the assessments by the various expert groups (Table 12). Most of the assessments do not discuss or conclude whether the carcinogenic mode of action has a threshold or not. MAK (2007) and ANSES (2014) indicate a non-threshold mode of action, however, giving very little, if any discussion on this.

Table 12: Overview of expert group findings of the carcinogenic potential and mode of action of the cobalt salts (Larsen *et al*, 2015)

Expert evaluation	**Carc.**	**Muta.** ***In vitro / in vivo****	***Mode of action****	**Carc. threshold / non-threshold**	**Cancer POD; Reference**	**Critical effect; POD; (Reference)**
ATSDR (2004)	+ inhalation	+/+ oral + i.p.	*ROS*	No discussion	-	Reduced lung function, humans NOAEL: 0.0058 mg Co/m^3 Occupational exposure, metallic cobalt (Nemery *et al*, 1992)
Swedish Work and Health SWH (2005a+b)	+ inhalation	+/+ oral + i.p.	*ROS (DNA repair)*	No discussion	-	Respiratory tract irritation, humans LOAEL: 0.003 mg Co/m^3 Occupational exposure, hard metal (Alexanderson 1979)
IARC (2006)	+ inhalation + i.p.	+/+ i.p.	*ROS* *DNA repair*	No discussion	-	Not assessed
WHO/CICAD (2006)	+ inhalation	+/+ oral + i.p.	*ROS* *DNA repair*	No discussion but attempt was made regarding low-dose risk estimation	BMDL10 (male mice): 0.358 mg Co/m3 (NTP, 1998)	Reduced lung function, humans NOAEL: 0.0058 mg Co/ m ^{3} Occupational exposure, metallic cobalt (Nemery *et al*, 1992)
MAK (2007) + **MAK (2009)**	+ inhalation also relevant for dermal exposure route	+/+ oral + i.p.	*ROS (DNA repair)*	No threshold could be derived in relation to genotox and cancer	-	Various effects on the respiratory tract: various LOAELs presented No specific POD
EFSA (2009) + **EFSA (2012)**	+ inhalation	+/+ oral + i.p.	*ROS (DNA repair)*	No discussion	-	Polycythaemia LOAEL (oral): 1 mg Co/kg (ATSDR 2004)
ECHC (2011)	+ inhalation	+/+ oral + i.p.	*ROS (DNA repair)*	No direct interaction between	-	Reduced lung function, humans NOAEL:

Expert evaluation	**Carc.**	**Muta.** ***In vitro/ in vivo****	***Mode of action****	**Carc. threshold / non-threshold**	**Cancer POD; Reference**	**Critical effect; POD; (Reference)**
				Co(II) and genetic material. MoE approach to be used		0.0058 mg Co/ m^3 Occupational exposure, metallic cobalt (Nemery *et al*, 1992) Cardiomyopathy, humans, LOAEL (oral): 0.04 mg/kg-bw/day (ATSDR 2004); (WHO/CICAD 2006)
Danish EPA (2013)	+ inhalation other exposure routes not excluded	+/+ oral + i.p.	*ROS;* *(DNA repair)*	No discussion	-	Polycythemia, humans LOAEL (oral): 1 mg/kg/d (Davis and Fields, 1958)
NTP (2013)	+ inhalation (cobalt metal)	+/+ inhalation	*ROS* *(K-ras mutations)*	No discussion	-	-
NTP (2014)	+ inhalation (cobalt sulphate)	+/not addressed	*ROS* *DNA repair*	No discussion	-	-
OECD (2014a+b)	+ inhalation	+/- oral	*ROS*	Threshold approach as not genotoxic *in vivo*	BMDL10 (female rats): 0.414 mg/m^3 as cobalt sulfate heptahydrate (NTP 1998)	Cobalt asthma, humans NOAEC:0.12 mg Co/m^3 (Sauni *et al*, 2010)
ANSES (2014)	+ inhalation	Metallic cobalt concluded as a weak genotoxic substance	*ROS* *(DNA repair)*	Non-threshold	Uncertain	Cancer/ inflammation. *Pragmatic* 8-h occupational limit value of 2.5 µg Co/m3 based on a BMDL10 (inflammation, rats) of 0.07 mg Co/m3

Expert evaluation	**Carc.**	**Muta.** ***In vitro/ in vivo****	***Mode of action****	**Carc. threshold / non-threshold**	**Cancer POD; Reference**	**Critical effect; POD; (Reference)**
REACH CSR (2014)	+ inhalation	+/- oral (inhalation metallic Co)	*ROS* *(Non-DNA damage*	Threshold approach as not genotoxic *in vivo*	BMDL10 (female rats): 0.414 mg/m^3 as cobalt sulphate heptahydrate (NTP 1998)	DNEL (workers, long-term): 0.105 mg/m^3 based on repeated dose toxicity DNEL (general population, long-term): 0.0166 mg/m^3 based on cancer - both as cobalt sulphate (DNEL values as reported in public version of REACH registration of cobalt sulphate)

*+/- indicates positive/negative conclusion regarding genotoxicity
**Mode of action set in ( ) indicates that the mode of action was only briefly mentioned

ECHC (2011), OECD (20145a+b), the REACH CSR (2014) and the recent review by Kirkland *et al* (2015) did not consider the cobalt salts to be genotoxic *in vivo*. In general, they concluded on a threshold mode-of-action as they considered ROS generation and impaired DNA repair as mechanisms with a threshold (however, without giving further specific data/documentation for this assumption).

In the information provided by CDI/CoRC (2015) in the context of the development of the dose-response relationship for the cobalt salts, it was acknowledged that specific data demonstrating a threshold for carcinogenic effects were lacking. However, it was argued (based on general assumptions) that the ROS initiating process in relation to DNA damage should be considered a threshold mode of action. For DNA-repair impairment, specific data on cobalt salts were forwarded indicating a threshold mechanism. Also, they found that the histopathological findings in the NTP (1998) studies could be explained by a cascade of effects, all of which could be considered as events with a threshold. Thus, alveolar proteinosis, chronic inflammation, hyperplasia of the alveolar epithelium, and hyperplasia of the bronchiolar epithelium could be interpreted to represent site-specific, steps in the formation of tumours. The sequential occurrence of these key events was also considered to be in accordance with the assumed mode of action regarding ROS generation and oxidative DNA damage. Nevertheless, it was stated that uncertainties remain to the exact mechanisms of the alterations in the alveolar and bronchiolar epithelia and to the disturbances of the control of regenerating cell proliferation leading to carcinogenesis.

Overall, it has to be noted that specific thresholds remain to be identified for the cobalt (II) ion with respect to tumour formation. Mechanistically, uncertainties pertain to whether the initial event of a catalytic effect of the cobalt (II) ions leading to oxidative DNA damages through a Fenton-like mechanism can be considered a threshold or a non-threshold effect. Further it is not clear whether the induction of alveolar proteinosis, chronic inflammation, hyperplasia (all of which may be considered as thresholded events) are prerequisite for the development of a carcinogenic response of cobalt (II).

When considering the REACH Guidance R.7a[12], it is stated that impairment of DNA repair *may* lead to genotoxicity via a non-linear or threshold dose response. In addition, it is stated that thresholds *may* be present for certain carcinogens that cause genetic alterations via indirect effects on DNA as a result of interaction with other cellular processes, e.g. cellular processes where the compensatory capacity or physiological or homeostatic control are exceeded. Also, it is recognised that for certain genotoxic carcinogens causing genetic alterations, a practical threshold *may* exist for the underlying genotoxic effect. For example, this has been shown to be the case for aneugens (agents that induce aneuploidy – the gain or loss of entire chromosomes to result in changes in chromosome number), or for chemicals that cause indirect effects on DNA that are secondary to another effect (e.g. through oxidative stress that overwhelms natural antioxidant defence mechanisms). The word "may" in the wording of the sentences indicates that a threshold cannot be concluded *per se,* but that such a conclusion has to be supported by data in a specific case.

In the context of a risk management decision under REACH, the scientific weight of evidence has to be weighed against the remaining uncertainties. The REACH Guidance R.8[13] emphasises that "*the decision on a threshold and a non-threshold mode of action may not always be easy to make, especially when, although a biological threshold may be postulated, the data do not allow identification of it. If not clear, the assumption of a non-threshold mode of action would be the prudent choice*". Lack of sufficient documentation and existence of remaining uncertainties would lead to the use of the most cautious approach for assessing genotoxic carcinogens, i.e. the non-threshold approach.

RAC (ECHA, 2016) has concluded that:

- Carcinogenicity data of the cobalt salts are only available for local tumours in the respiratory tract in relation to inhalation exposure, thus dose response estimations can only be made for inhalation exposure.
- The current scientific findings and mode of action considerations support the notion that water soluble cobalt substances may be threshold carcinogens although there are some uncertainties related to initiation by catalytic ROS generation and direct oxidative DNA damage. In addition, the genotoxicity data may indicate a non-threshold mechanism.
- Thresholds have not been identified for the cobalt salts in relation to the carcinogenicity and genotoxicity in the respiratory tract.

Therefore at present, due to lack of identified thresholds and due to remaining uncertainties regarding the mechanisms involved, the cobalt salts are considered as genotoxic carcinogens and are to be assessed using a non-threshold approach. *Information regarding genotoxicity and mode of action submitted in the public consultation*

According to the comments provided by the cobalt industry in the public consultation of this restriction proposal, the cobalt salts are non-genotoxic (or non-direct genotoxic) and exhibit a threshold in the dose-response. A value of 5 µg/m3 for the respirable fraction is proposed for the threshold. In their comments, the cobalt industry state that new data is available that support this view and that was not taken into account by RAC in their previous assessment of cobalt compounds (ECHA, 2016; ECHA 2017b).

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[12] Guidance on information requirements and chemical safety assessment, Chapter R.7a: Endpoint specific guidance (version 3.0)

[13] Guidance on information requirements and chemical safety assessment, Chapter R.8: Characterisation of dose [concentration]-response for human health (version 2.1)

The industry identifies this new information as originating from ToxTracker reports and several articles:

a) ToxTracker reports: one in Appendix 1 of the industry position paper; a second report in the paper Cappellini et al, 2018;

b) Articles by Smith and Perfetti, 2018; Lison *et al*, 2018; Marsh *et al* 2017; Sauni *et al* 2017; Yong *et al* (in preparation).

A study report based on Toxtracker (confidential, 2019) was provided which shows that cobalt fine powder and cobalt dichloride hexahydrate do not induce any DNA damage but generate oxidative stress and hypoxia. However, the adequacy of the study and results cannot be assessed as no materials and methods details were available. It should be noted that, according to information obtained in June 2019 from OECD (Nathalie Delrue) and ECVAM (Raffaella Corvi), the ToxTracker method has not yet been validated. While an OECD SPSF was submitted with accompanying documents (available on site for OECD Test Guidelines: https://community.oecd.org/docs/DOC-57088 , see Project 4.125), the validation study is still ongoing and no validation report is available yet. A previous study report based on Toxtracker results by Cappellini *et al* (2018) showed that cobalt (metal) nanoparticles (NPs) induced reporters related to oxidative stress and DNA strand breaks and that cobalt oxide CoO NPs produced similar but weaker effects (whereas cobalt oxide Co3O4 nanoparticles were inactive). In general terms, the data from ToxTracker (both the Capellini report and the confidential Toxtracker report submitted by industry) seem to support the claim that cobalt compounds induce oxidative damage. However, it need to be stressed that data cannot be considered as validated data.

Regarding the articles submitted, the one by Smith and Perfetti (2018) does not focus on cobalt (the word 'cobalt' is not mentioned once in the paper) and does not provide any substance specific argument to support the claim of the industry in relation to cobalt salts. This paper only makes some general statements in relation to the fact that "sometimes testing non-genotoxic chemicals at high doses induces cytotoxicity which leads to tumour formation via amplification of background mutation rates…" and "that oxidative stress is […] tends to be induced in rodents at high doses frequently not relevant to humans".

The review of Lison *et al* (2018) summarised recent genotoxicity and carcinogenicity data, for inorganic and organic salts and oxides and for metallic cobalt. Concerning soluble cobalt salts, most of the recent genotoxicity data originated from the paper of Kirkland et al (2015) where several in vitro and in vivo OECD-compliant studies were carried out with different cobalt compounds in different CROs. It is noted that this paper was taken into account by RAC in their previous assessments of the cobalt compounds (ECHA, 2016; ECHA 2017B).

Concerning carcinogenicity of cobalt compounds, the recent studies mentioned by Lison *et al*. are Sauni *et al.* (2017) and Marsh *et al* (2017). It is noted that both studies are cited in the RAC opinion on the classification and labelling of cobalt metal (ECHA, 2017b) and further discussed in section B.4.4.2 of this restriction dossier.

The review by Lison et al (2018) concluded that 1) the genotoxic activity of soluble cobalt salts and oxides are driven by the Co(II) ions released by dissolution; and 2) the mechanisms mediating the genotoxicity and carcinogenicity, which include indirect genotoxicity (ROS production, inhibition of DNA repair), are expected to exhibit a practical threshold.

In relation to the conclusions of Kirkland *et al* (2015) and Lison *et al* (2018), the Dossier Submitter would like to stress that, although the data provided demonstrate that cobalt salts induce the production of ROS that cause oxidative DNA damage (as shown by reduction in DNA damage by NAC treatment, or by DNA damage increase in comet assay when using specific enzymes), they do not demonstrate that cobalt compounds induce DNA damage exclusively via an oxidative mechanism (e.g. in Kirkland *et al* 2015, an increase in DNA damage, i.e. DNA single and double strand breaks and alkali labile sites, is indeed also observed in the standard comet assay, which cannot be directly explained by oxidative mechanism).

The last paper cited as ‘new’ data in the industry position document was Yong et al. (manuscript for publication in preparation). It is noted that, although this document quotes this manuscript and provide some hypothesis (e.g. that ‘the biological threshold is above the exposures experienced by the workers in the observed cohorts’), no additional information (e.g. title, authors) was provided regarding this reference and this reference will not be commented here. And I did not manage to identify such article among the published papers up to July 2019.

In conclusion, the information submitted by industry support the assumption that cobalt salts induce oxidative DNA damage. In case the genotoxicity caused by the cobalt salts were exclusively due to oxidative damage, it would imply that cobalt salts would be indirect genotoxicants with a mode of action with a threshold. However, the data provided does not show that cobalt compounds induce DNA damage exclusively via an oxidative mechanism. Almost on the contrary, the in vitro comet assay data in Kirkland *et al* 2015 seem to show that a significant (at least non-negligible) part of the genotoxicity induced by cobalt compounds is not directly explained by oxidative damage or another threshold mechanism. Therefore, the data provided is not sufficient to demonstrate that the cobalt salts induce an indirect genotoxic effect and that the mode of action presents a threshold.

B.4.5. Dose-response relationship

In 2016 RAC agreed on a dose-response relationship for the cobalt salts (ECHA, 2016). The point of departure (POD) for the dose response assessment is based on the findings from the NTP (1998) inhalation studies in which mice and rats were exposed to cobalt sulphate heptahydrate by inhalation. From these data, OECD (2014a) calculated benchmark doses (BMD) using the US EPA BMD software (Version 2.0) with the Gamma Model (Version 2.13). The numbers of alveolar/bronchiolar adenoma or carcinoma in the lungs of rats and mice were selected as benchmark response. The 95 % lower confidence limit of the BMD for a treatment-related increase in response of 10 % was calculated (BMDL10). The lowest BMDL10 value of 0.414 mg/m^3 was found for female rat tumours.

When converting this dose level to cobalt (II) levels, it further has to be taken into account that chemical analysis showed that exposure in fact was to cobalt sulphate hexahydrate and *not* the heptahydrate (NTP, 1998). Thus, using the molecular weights of cobalt sulphate hexahydrate (263.10 g/mol) and cobalt (58.83 g/mol) a BMDL10 of 0.093 mg Co/m^3 was derived by OECD (2014a).

As the animals in the NTP (1998) were exposed to cobalt sulphate particles with a MMAD (Mass Median Aerodynamic Diameter) in the range of 1 µm – 3 µm, and as the lung tumours from which the BMDL10 level were derived were located in the deeper part of the lung, the dose-response relationships below are related to the respirable fraction of the particles.

Dose response relationships were derived by linear extrapolation, which is to be considered as a very conservative approach, especially at very low exposure levels. It is acknowledged therefore that excess risks in the lower exposure range might be overestimated following this approach.

The BMDL10 value of 0.093 mg Co/m^3 was calculated in association to lifetime exposure of female rats (6h/d, 5d/week, for 105 weeks). For conversion of the daily exposure concentration, the converted BMDL10 value can be calculated according to ECHA Guidance [14] by using the following factor:

BMDL10 (daily exposure) = BMDL10 (mg Co/m^3) x (6h/d / 8h/d) x (6.7 m^3 * / 10m^3 **)

> *average inhalation volume of humans during 8h (comparable to situation of the experimental animals)
>
> **inhalation volume of worker during 8h light activity

BMDL10 (daily exposure) = 0.093 mg Co/m^3 x (6h/d / 8h/d) x (6.7 m^3/10m^3)

BMDL10 (daily exposure) = 0.047 mg Co/m^3

The linearized approach described by the ECHA Guidance will be used for the non-threshold approach. When making risk calculations for occupational exposure levels, a correction has to be done to account for the fact that workers are only exposed during a fraction of their life (48 weeks per year during 40 years of work life) compared to the experimental animals that were exposed throughout their lifetime).

BMDL10 (occup. exposure) = BMDL10 (daily exp) x (52w / 48w) x (75y / 40y)

BMDL10 (occup. exposure) = 0.047 mg Co/m^3 x (52w / 48w) x (75y / 40y) = 0.095 mg Co/m^3

This BMDL10 (occup. exposure) should not be subject to the use of further assessment factors before scaling down to low level exposure, as an allometric assessment factor is only used for dose metrics expressed in mg/kg/d and not inhalational dose metrics expressed in mg/m^3.

Thus, from a risk level of 0.1 at a dose of 0.095 mg Co/m^3, a linear extrapolation for the dose response relationship for excess cancer risk can be made down to zero risk and zero exposure. The risk can be calculated by the slope of the curve = 0.1 / 0.095 mg Co/m^3 = 1.05 (mg Co/m^3)$^{-1}$, resulting in the following dose-response function:

Excess risk (lung cancer, workers) = 1.05 (mg Co/m^3)$^{-1}$ x exposure level (respirable fraction)

Inhalable particles would - for the particle fraction above the size of the respirable range – to a great extent be deposited in the upper part of the respiratory tract where it can be absorbed directly into the blood after dissolution or moved into the gastrointestinal tract by mucociliary action. NTP (2016) studies with cobalt and cobalt sulphate suggest that soluble fractions of cobalt appear to be multi-site rodent carcinogens following inhalation exposure. Carcinogenicity effects in the respiratory system as well as in the adrenal glands, blood and pancreas have been found following exposure to cobalt metal of rats and mice. Exposure to cobalt sulphate resulted in tumours in the lungs and in the adrenal glands. However, although inhalable particles should be considered as carcinogenic, the dose-response related to this metric is far more uncertain as this will very much depend of the content of respirable particles (ECHA, 2016).

Based on these findings, the Dossier Submitter concludes that exposure to the non-respirable fraction of the cobalt salts will increase the excess cancer risk of workers. Since there is no quantified metrics available to determine the excess cancer risk from the non-respirable

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[14] ECHA Guidance on information requirements and chemical safety assessment Chapter R.8: Characterisation of dose [concentration]-response for human health (ECHA, 2012)

fraction, the Dossier Submitter will apply the dose–response relationship derived above to the inhalable fraction of the cobalt salts as a precautionary approach.

The following individual excess lifetime cancer risks are derived based on a lifetime worker inhalation exposure (8h/day, 240 days/year, 40 years):

Exposure levels (µg Co/m³)	**Excess lifetime cancer risk in workers**
100	1.05×10^{-1}
10	1.05×10^{-2}
1	1.05×10^{-3}
0.1	1.05×10^{-4}
0.01	1.05×10^{-5}

In the public consultation the cobalt industry identified the study by Suh *et al* (2016) which had not been previously considered by the Dossier Submitter. The study focuses on the derivation of a dose-response metric for cobalt metal. According to the authors "the mechanistic data support that the carcinogenic mode of action (MoA) is likely to involve oxidative stress and thus non-linear /threshold mechanisms. However the lack of a detailed MoA and the use of high toxic exposure concentrations in the bioassay preclude derivation of a reference concentration protective of cancer. Several analysis resulted in an IUR [inhalation unit risk] of 3.4×10^{-3} per µg/m³ for cobalt metal". The Dossier Submitter would like to stress that this is in line with the RAC agreement in 2016 and the restriction report. It is also worthy to note that the Dossier Submitter has estimated an inhalation unit risk of 1.05×10^{-3} per µg/m³ for the cobalt salts which is in a similar order of magnitude to the value calculated for cobalt metal by Suh *et al*.

B.9. Exposure assessment

B.9.1. General discussion on releases and exposure

B.9.1.2. Summary of the existing legal requirements

In addition to the requirements under REACH, the primary legal requirements affecting exposure to the cobalt salts relate to the need to control exposure under European occupational health and safety legislation. In particular, Directive 2004/37/EC requires employers to[15]:

- Assess and manage the risk of exposure to carcinogens or mutagens.
- Reduce the use of the substances by replacing them with substances not dangerous or less dangerous.

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[15] Directive 2004/37/EC - carcinogens or mutagens at work, https://osha.europa.eu/en/legislation/directives/directive-2004-37-ec-carcinogens-or-mutagens-at-work, accessed 31/03/2018.

- Prevent workers' exposure. If replacement is not possible, use closed technological systems.
- Where a closed system is not technically possible, reduce exposure to minimum (and to a level not exceeding limit values set out in Annex III of the Directive).

Wherever carcinogens or mutagens are used, employers are required to:

- Limit the quantities at the place of work.
- Keep the number of workers exposed as low as possible.
- Design the work processes so as to minimise the substance release.
- Evacuate carcinogens or mutagens at source, taking into account the environment.
- Use appropriate measurement procedures (especially for early detection of abnormal exposures from an unforeseeable event or accident).
- Apply suitable working procedures and methods.
- Implement the use of individual protection measures if collective protection measures are not enough.
- Provide for hygiene measures.
- Demarcate risk areas and use adequate warning and safety signs (including "no smoking").
- Use of sealed and clearly and visibly labelled containers for storage, handling, transportation and waste disposal.
- Draw up emergency plans.
- Provide appropriate training to workers, including information and instructions regarding potential risks to health, precautions to prevent exposure, hygiene requirements, protective equipment and clothing, and the handling of incidents.

Table 13 summarises known information on existing OELs for the cobalt salts within the scope of this restriction dossier.

Table 13: Existing national OELs for cobalt compounds

Member state	**Cobalt sulphate (CAS 10124-43-3) Limit value 8h (mg Co/m³)**	**Cobalt dichloride (CAS 7646-79-9) Limit value 8h (mg Co/m³)**	**Cobalt and compounds Limit value 8h (mg Co/m³)**	**Cobalt and compounds Limit value short term (mg Co/m³)**
Austria			0.1	0.4
Belgium			0.02	
Denmark			0.01	0.02
Finland	0.02	0.02	0.02	

Member state	**Cobalt sulphate (CAS 10124-43-3) Limit value 8h (mg Co/m³)**	**Cobalt dichloride (CAS 7646-79-9) Limit value 8h (mg Co/m³)**	**Cobalt and compounds Limit value 8h (mg Co/m³)**	**Cobalt and compounds Limit value short term (mg Co/m³)**
Hungary			0.1	0.4
Ireland			0.1	
Latvia			0.5	
Norway			0.02	
Poland			0.02	
Slovakia			0.05	
Spain			0.02	
Sweden	0.02	0.02	0.02	
The Netherlands			0.02	
United Kingdom			0.1	
Source: GESTIS international limit values, http://limitvalue.ifa.dguv.de/WebForm_gw2.aspx, accessed 26/02/2018. Note OELs are not listed for cobalt dinitrate, cobalt carbonate and cobalt di(acetate).				

Germany has established an acceptable concentration of 0.5 µg/m3 and a tolerable concentration of 5 µg/m3 for cobalt and cobalt compounds classified as Carc. 1A, Carc. 1B (alveolar fraction) (TRGS 561).

B.9.1.3. Summary of the effectiveness of the implemented operational conditions and risk management measures

The cobalt salts are widely used in different sectors and processes, and under different operational conditions. Reaction processes take place in closed systems while transfer operations, mixing and packaging take place either in closed, semi-closed or open systems depending on the use (CoRC, 2018).

The exposure scenarios from the registration dossiers (CoRC, 2018) identify the use of local exhaust ventilation (LEV) for certain activities with a minimum effectiveness specified between 78% and 90%. The use of respiratory protective equipment (RPE) is recommended for specific tasks, with an APF[16] ranging between 10 and 40.

Additionally, the following risk management measures are identified for each of the task/activities included in the exposure scenarios:

- Protective gloves according to EN 374 should be worn at all workplaces unless any exposure to the substance can be excluded. Gloves have to be changed according to manufacturer's information or when damaged, whatever is the earlier. Continuous

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[16] Assigned protection factor according to EN 529

supervision and training of workers wearing gloves is required. Face protection needs to be worn as appropriate.

- Good occupational hygiene practices are required to ensure a safe handling of the substance including measures (e.g. shower and change clothes at end of work shift) to avoid any contamination of private households via the work-home-interface and housekeeping practices (i.e. regular cleaning with suitable cleaning devices), no eating and smoking in the workplace.
- Unless otherwise stated, certified working clothing and shoes should be worn during work. Any contaminated clothing should not be taken home.
- Good general ventilation in the workplace should be ensured. Dust should not be blown off (e.g. from dried splashes) with compressed air.
- Regular training in workplace hygiene practice and proper use of personal protective equipment (if relevant) is required.

The operational conditions, specific risk management measures, and worker inhalation exposure levels for each of the uses are presented in detail in the following sections.

B.9.2. Manufacturing

B.9.2.1.Overview of manufacturing processes and exposure

The cobalt salts are manufactured through the processing of a variety of cobalt-containing raw materials, including other cobalt salts (mainly cobalt carbonate). The specific manufacturing processes may vary depending on which cobalt salt is being produced and are discussed in more detail section A.1.2.

In general terms, the manufacturing process involves taking the raw material as powder, chips or bulk material (CoRC, 2017) and then processing through a series of wet and hot metallurgical processes, including acid leaching, solvent extraction, precipitation, filtration, crystallisation and drying. Once the cobalt salts are produced they are further processed to refine the material into a finished product through milling and sieving. The final compounds can be produced as both powders and solutions for use / distribution. The main steps of the manufacturing process are presented in Table 14 below.

Table 14: Processes involved in the manufacture of cobalt salts (CoRC, 2018)

Exposure Scenario	Tasks	Form of cobalt salt	Cobalt salt content
Raw material handling	Raw material handling, reactor loading, immediate removal of wet splashes	Solid, powder / dust ; Aqueous solution ; Massive object	Not restricted
Preparation of raw material	Weighing, sampling, acid leaching, dissolving, filtration, scraping, purification, cementation, de-ironing (hydrolysis)	Aqueous solution	Not restricted
Reaction[1]	Wet process, dry process, mixing, dissolving, precipitation, separation, filtration,	Aqueous solution	Not restricted

Exposure Scenario	Tasks	Form of cobalt salt	Cobalt salt content
	pumping, cleaning, unloading, reaction, stripping, extraction, formulation		
Wet process	Solvent extraction, back stripping, precipitation, drying	Aqueous solution	Not restricted
Hot process	Pyrolysis, calcination	Solid ; Aqueous solution	Not stated
Further processing	Blending, milling, sieving	Solid, powder/dust ; Aqueous solution	Not stated
Filling of liquids / solutions	Filling, immediate removal of wet splashes.	Aqueous solution	Not restricted
Filling of liquids/solutions in closed system	Filling of solutions in closed system, control walks, supervision and adjusting machinery	Aqueous solution	Not restricted
Packaging of low and/or medium dusty materials[1]	Packaging	Solid, pellet / pastille	Not restricted
Handling of powders with moderate dustiness potential	Drying, packaging.	Solid, powder / dust	Not restricted
Handling of powders with high dustiness potential	Packaging	Solid, powder / dust	Not restricted
Cleaning and maintenance	Manual cleaning, repair and maintenance operations, removal of residuals from e.g. filters/overspill or as waste	Solid, powder / dust	Not restricted

[1] Cobalt di(acetate) only

B.9.2.2. Worker exposure

Estimates of inhalation exposure and details of risk management measures applied for the manufacture of cobalt salts are set out in Appendix 3, based on the exposure scenarios of the registration dossiers (CoRC, 2018). The highest exposure levels are reported in the 'further processing' step (blending, milling, sieving) and 'handling of powder' (including packaging), with air concentration levels (RWC)[17] based on personal samplers estimated as 239 µg Co/m^3 and 808 µg Co/m^3 respectively. Respiratory protection with a minimum APF of 20 is specified for these steps and, when RPE and exposure duration are taken into account, the exposure estimates are 7 µg Co/m^3 and 6 µg Co/m^3 respectively.

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[17] RWC: Reasonable Worst case estimate based on the 90th percentile of the exposure data.

B.9.2.3. Risk management approaches

An overview of the risk management measures specified in the exposure scenarios of the registration dossiers for the different process steps in the manufacture of cobalt salts is provided in Appendix 3. The preparation of raw materials, wet process, hot process, further processing and filling of solutions take place in fully contained systems. Additionally, the preparation of raw materials, reaction, wet process, hot process, further processing and handling/packaging of powders and dusts require the use of LEV (minimum 85% effectiveness) and RPE.

Manufacturing/importers of cobalt salts report the introduction of engineering control-related risk management measures over the last five years (eftec, 2018b), including automated packing stations for powder; containment for mixing lines; use of water solutions; upgraded fume hoods and air filters; replacement and optimisation of central ventilation system, etc. It is understood that these relate to a selection of different controls implemented by different companies. As outlined in the eftec (2018b) report, administrative controls have been also implemented, including: regular air monitoring programmes and staff rotation. Some companies report the introduction of PPE as a control measure to reduce worker exposure. According to industry, the introduction of these measures have resulted in a reduction of exposure to workers (eftec, 2018b). However, the reduction levels have not been reported.

In a specific survey conducted for the development of this restriction dossier (see annex G), two manufacturers of cobalt salts report the use of LEV with a 95% to 99% effectiveness in those processes not fully enclosed and the use of RPE with an APF from 20 to 40. RPE (APF =40) is also specified for cleaning and maintenance. According to the respondents these risk management measures are representative for their sector of activity. One respondent further specifies that the process operates in many parts under negative pressure to ensure the effective containment of the substance.

B.9.3. Manufacture of chemicals (intermediate use)

B.9.3.1. General information

The cobalt salts are used as intermediates to manufacture other chemical compounds, such as inorganic cobalt compounds and cobalt carboxylates. These uses encompass the following categories listed in Table 15 (shown below).[18]

Table 15: Overview of uses for chemicals sector

Number	Identified use
1	Manufacture of chemicals
2	Manufacture of carboxylates and resonates

An overview of the different production stages as presented in the exposure scenarios from the registration dossiers (CoRC, 2018) are provided below (Table 16).

Table 16: Processes involved in the manufacture of chemicals (CoRC, 2018)

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[18] For the purposes of this dossier the manufacture of cobalt compounds to be used as intermediates in the production of catalysts, batteries, pigments and dyes are considered under separate sections.

Exposure Scenario	Tasks	Form of cobalt salt	Cobalt salt content
Raw material handling	Loading/unloading, weighing, immediate removal of wet splashes.	Solid, powder / dust ; aqueous solution	Not restricted
Mixing/Reaction [1)]	Wet process, mixing, dissolving, precipitation, separation, filtration, reaction, stripping, extraction, sampling.	Aqueous solution	Not restricted
Hot Process [1)]	Pyrolysis, calcination	Solid/ aqueous solution	Not restricted
Cleaning and maintenance	Manual cleaning, repair and maintenance operations, removal of residuals from e.g. filters/overspill or as waste	Solid, powder / dust	Not restricted
[1)]The substance is chemically transformed into another substance at this step of the process			

B.9.3.2. Worker exposure

Information on numbers of sites in the EU using cobalt salts in the chemicals sector has been provided by eftec (2018a). This is shown in Table 17 below.

Table 17: Numbers of sites and workers for the manufacture of chemicals in the EU (eftec, 2018a)

	Estimate	Mean (range) per DU
Number of downstream users	44	-
Total volume used	26 600 tonnes	<600 tonnes (<100-20 200)
Total number of workers exposed	4 900 (7%)	100 (<100-1 400)
Total number of workers employed	67 600	1 500 (<100-45 000)
Note: The information provided by eftec (2018a) is based on the three following uses: production of chemicals / manufacture of chemicals in wet-chemical processes; manufacture of cobalt carboxylates resonates; and production of cobalt compounds used in battery manufacture. Figures are rounded to avoid impression of false accuracy.		

Upon receipt of the cobalt salts the user industries begin with the handling of materials to be added to the subsequent processes. Depending on the operators, the cobalt salts are supplied as either a powder or an aqueous solution. It is to be noted that the manufacture of chemicals is an intermediate use and therefore the following steps of the process, once the cobalt salt is transformed into another cobalt compound are not further considered in the exposure scenarios from the registration dossiers, although they may be a source of further worker exposure to cobalt.

Estimates of inhalation exposure and details of the risk management measures applied for the chemicals sector, as identified in the exposure scenarios of the registration dossiers, are set out in Appendix 3. The highest exposure levels are reported for raw material handling, with air concentration levels based on personal samplers estimated between 168 to 206 µg Co/m^3 (RWC). Taking into account the use of RPE and the duration of the activity, the RWC (8h TWA) exposure estimates vary from 6 to 10 µg Co/m^3 for this activity. Air concentration levels for activities involving the use of aqueous solutions are significantly lower, from 2 to (RWC), resulting in exposure estimates from 0.1 to 2 µg Co/m^3 (RWC 8 h TW).

B.9.3.3. Risk management approaches

An overview of the risk management measures specified for the different uses of cobalt salts is provided in Appendix 3, based on the exposure scenarios of the registration dossiers. It is noted that, the mixing and reaction stages takes place in closed systems while the use of LEV (minimum 85% effectiveness) and RPE (APF=10-20) are specified for raw material handling.

The dossier submitter has not been able to validate this information through other sources.

B.9.4. Manufacture of batteries (intermediate use)

B.9.4.1. General information

The cobalt salts are used as intermediates in the manufacture of other cobalt compounds used in the production of batteries. Table 18 below shows an overview of the process steps as presented in the exposure scenarios from the registration dossiers (CoRC, 2018).

Table 18: Processes involved in the production of cobalt compounds used in battery manufacture (CoRC, 2018)

Exposure Scenario	**Tasks**	**Form of cobalt salt**	**Cobalt salt content**
Raw material handling	Powder handling, weighing, immediate removal of wet splashes	Solid, powder / dust	Not restricted
Mix preparation [1)]	Metal leaching, mixing	Aqueous solution	Not restricted
Cleaning & Maintenance	Manual cleaning, repair and maintenance operations; Removal of residuals from e.g. filters/overspill or as waste.	Solid, powder / dust	Not restricted

[1)] The substance is chemically transformed into another substance at this step of the process

B.9.4.2. Worker exposure

There are more than 20 plants identified in Europe that use the cobalt salts as the starting material for the manufacture of cathodic material for batteries, although several of them have limited production, for niche or specialty markets. The exact number of workers exposed to cobalt salts in this sector is not known but according to industry it could be estimated at below 100 workers (CI, 2018). It is to be noted that approximately 1 500 workers are expected to be exposed to cobalt-containing substances (including the cobalt salts) in the manufacturing and recycling of batteries. No figure has been provided regarding the volumes of the cobalt salts in use in this sector.

Estimates of inhalation exposure are set out in Appendix 3, based on the exposure scenarios of the registration dossiers (CoRC, 2018). Air concentration levels (RWC) for 'raw material handling' (powder) and 'mix/preparation' (aqueous solution) based on personal samplers are estimated as 153 µg Co/m^3 and 29 µg Co/m^3 respectively. Respiratory protection with a minimum APF of 10 is specified for 'raw material handling' and, when RPE and exposure duration are taken into account, the exposure estimates (RWC 8h TWA) are around 1 µg Co/m^3 for both steps.

B.9.4.3. Risk management approaches

An overview of the RMMs specified for the different process steps is provided in Appendix 3. The 'mix/preparation' step takes place in a closed semi-automated process with integrated LEV (90% effectiveness) while for 'raw material handling' no specific engineering measures are recommended. The use of RPE (APF 10 to 40) is required for all process steps where exposure to cobalt salts in powder form is expected.

No further information on the conditions of use of the cobalt salts in this sector of use is available to the Dossier Submitter.

B.9.5. Manufacture of catalysts (intermediate use)

B.9.5.1. General information

Table 19 provides an overview of the different production stages in the manufacture of catalysts as presented in the exposure scenarios from the registration dossiers (CoRC, 2018).The responses to the call for evidence from several companies and the sector organisation provide some additional information on these activities as well as information submitted in a survey conducted by ECHA for the purpose of developing this restriction dossier (see annex G).

Table 19: Processes involved in the production of catalysts (CoRC, 2018)

Exposure Scenario	Tasks	Form of cobalt salt	Cobalt salt content
Delivery and storage of raw material	Delivery, transfer, storage	Solid, powder / dust (carbonate and dinitrate) ; aqueous solution (dinitrate only)	Not restricted
Dissolution of raw material	Addition of reagents, dissolution, sampling	Solid, powder / dust, forming aqueous solutions	Not restricted
Impregnation and drying of raw material on carrier	Addition of reagents, impregnation, transfer to dryer, drying	Aqueous solution, Non-dusty solids (impregnated supports)	Not restricted
Filtration and drying of precipitate	Filtration, discharge of wet filter cake from filter unit, extrusion, transfer to dryer, drying	Wet filter cake; Slurry; Non-dusty solids	Not restricted
Calcination of precipitate/supports, or impregnated on support 1)	Transfer to calciner, calcination	Wet filter cake; Non-dusty solids	Not restricted

Exposure Scenario	**Tasks**	**Form of cobalt salt**	**Cobalt salt content**
Reduction of precipitate 1)	Transfer to reducer; reduction	Extrudates (Non-dusty solid)	Not restricted
Cleaning and maintenance	Manual cleaning, repair and maintenance operations; Removal of residuals from e.g. filters/overspill or as waste. Maintenance and repair work only at facilities which are not in operation. Minor cleaning tasks may be conducted under operation	Various	Not restricted

1) The substance is chemically transformed into another substance at this step of the process

Cobalt carbonate makes up approximately 70% by weight of the cobalt salts used in the manufacture of cobalt-containing catalysts (CfE 509). One company (CfE 509) note that cobalt carbonate is only available in the EU as a powdered product, and at their facility, the cobalt carbonate used is either manufactured on site (as an on-site isolated intermediate) or supplied as a transported isolated intermediate. Another company (CfE 516) also report that cobalt carbonate is delivered to the catalyst manufacturing sites as a powder. Cobalt carbonate is supplied either in bulk tankers or in big bags and is formulated into a solution at the catalyst manufacturing site. The process subsequently involves a series of wet and hot processes to transform the cobalt carbonate into another cobalt compound which is further used in the production of cobalt-containing catalysts.

Cobalt dinitrate is also used in the manufacture of cobalt-containing catalysts although to a lesser degree (CfE 509). One company (CfE 509) indicated that at their facility, cobalt dinitrate is manufactured on site (with cobalt metal as the starting raw material) or supplied as an isolated intermediate in an aqueous solution. Another company (CfE 516) indicated that at their facility, cobalt dinitrate is delivered either as an aqueous solution or as a crystalline, non-dusty solid. Subsequently the manufacturing process involves a series of wet and hot processes to convert the cobalt salts into other cobalt compounds (including cobalt carbonate) which are further used in the production of catalysts.

Similar to other intermediate uses, once the cobalt salt (either cobalt carbonate or cobalt dinitrate) is transformed into another cobalt compound, the following steps are not further considered in the exposure scenarios from the registration dossiers, although they may be a source of further worker exposure to cobalt.

B.9.5.2. Worker exposure

Information on numbers of sites in the EU using cobalt salts in the catalyst sector has been provided by eftec (2018a). This is shown in Table 20 below.

Table 20: Numbers of sites and workers for catalysts in the EU 28 (eftec, 2018a)

	Estimate	**Mean (range) per DU**
Number of downstream users	15	1 (1-2)
Total volume used	1 700 tonnes	110 (<10-540)

	Estimate	Mean (range) per DU
Total number of workers exposed	800 (19%)	60 (<10-140)
Total number of workers employed	4 100	290 (50-800)
Note: Figures are rounded to avoid impression of false accuracy		

Estimates of inhalation exposure and details of risk management measures applied for the use of cobalt salts in the manufacture of catalysts are set out in appendix 3 based on the exposure scenarios from the registration dossiers (CoRC, 2018). The highest air concentration levels (RWC) are reported for the 'calcination' step and the 'reduction' step with exposures based on personal samplers estimated around 20 µg Co/m^3. When the use of RPE (APF=20) and exposure duration are taken into account, the exposure estimates (RWC 8h TWA) are 0.03 and 3 µg Co/m^3 respectively.

B.9.5.3. Risk management approaches

An overview of the risk management measures at each process step of the manufacture of cobalt-containing catalysts using cobalt salts, as indicated by the exposure scenarios of the registration dossiers (CoRC, 2018) is provided in appendix 3.

It is noted that most of the process steps are semi- or predominantly contained. For some specific steps, the use of RPE (APF = 20) is identified. In the 'reduction' step, the use of LEV (90% effectiveness) is also recommended. This step gives the highest exposure levels in the process (see section B.9.3.2 above) but it is understood that the source of the cobalt exposure is an additional step of the process, i.e. 'screening', where the cobalt salt does not exist anymore but has been transformed into another cobalt compound.

One company (CfE 516) report that, during the catalyst manufacture process, standard prevention measures include safety and handling procedures for the preparation of solutions from the cobalt salts, and negative pressure in calciners and other rotary equipment to prevent escape of vapours and dust.

It can be observed in appendix 3, that the level of exposure reported during the handling and dissolution of raw materials in the manufacture of catalysts is significantly lower than observed for other sectors (e.g. the chemical sector), specifically for the use of the cobalt salts in powder form. This can be attributed to the containment of the process in most of the facilities operating with powder forms. For example, one company (CfE 516) report the use of a contained transfer system under LEV for the unloading operations of cobalt carbonate. According to this company, weighing, transfers and dissolution are all closed processes, remotely operated and with no direct contact between workers and cobalt carbonate in normal plant operation.

Companies (CfE 509; and CfE 516) report that cobalt dinitrate is delivered to catalyst manufacturing sites either as an aqueous solution or as a crystalline, non-dusty solid. The liquid raw materials are enclosed in pipework, and are directly transferred to the process equipment. Solid raw materials are transferred via a closed system to the processing equipment, then dissolved in a closed system to form an aqueous solution.

In a survey conducted by ECHA for the development of this dossiers, four respondents including the sector organisation report the use of fully contained systems and/or partially contained systems with LEV as representative conditions to control exposure to cobalt salts in solid form in this sector of use. However, according to two of the respondents, there are differing levels of implementation across the catalyst sector. For example, one respondent reports the unloading of big-bags by gravity in a closed room at their manufacturing site with operators wearing RPE as a control measure while other respondent identify the use of a contained transfer system under LEV for the handling of raw material in powder form. It is not fully clear to the Dossier Submitter whether the air concentration levels reported in the exposure scenarios (see section B.9.5.2 above) and the related exposure estimates reflect the varying conditions of use and levels of control of the cobalt salts in this use.

The sector organization (CfE 505) provided details of two programs in progress or in planning to reduce exposure that are company specific. Firstly, a ‘full dust reduction project’, with an estimated capital expenditure in the region of €1 to 10 million. It is currently in the scoping phase but it is expected to take between 5-10 years to complete. The specific detail of the project have not been provided. Secondly, another potential program included further engineering measures, whereby loading and transfer operations are completely in closed units with separated ventilation and additional robotics/automation. The technical feasibility of this project is still to be evaluated. However, according to the sector organization, the risk reduction potential may not be considered proportional to the estimated costs, and it would take 5-10 years to implement (from concept to implementation).

B.9.6. Manufacture of pigments and dyes (intermediate use)

B.9.6.1. General information

The following uses have been identified in the manufacture of pigment and dyes in the exposure scenarios of the registration dossiers (CoRC, 2018):

Table 21: Overview of uses for the manufacture of pigments and dyes

Number	**Identified use**
1	Manufacture of inorganic pigments, frits, ceramic ware, glass
2	Manufacture of dyes for textile, leather, wood and paper industry

However, it is not clear to what extent these two uses are still taking place. The only use identified so far in the stakeholder consultation in this sector corresponds to the use of cobalt sulphate in aqueous solution for the manufacture of inorganic pigments (see section A.2.5). In addition, according to the Cobalt Institute the cobalt salts are used in the manufacture of metal-complex dyes for the textile industry.

Table 22 below show the process steps identified for this exposure scenario.

Table 22: Processes involved in the manufacture of pigments and dyes (CoRC, 2018)

Exposure Scenario	**Tasks**	**Form of cobalt salt**	**Cobalt salt content**
Raw material handling	Weighing, filling of mixer/dryer	Aqueous solution	Not restricted
Reaction[1)]	Mixing and reaction, immediate removal of wet splashes	Aqueous solution	Not restricted
[1)]The substance is chemically transformed into another substance at this step of the process			

B.9.6.2. Worker exposure

Estimates of inhalation exposure for this sector are set out in appendix 3 based on the exposure scenarios from the registration dossiers (CoRC, 2018). The highest air concentration levels of cobalt are reported for the ‘raw material handling’ with measurements (RWC) based on personal samplers estimated as 29 µg Co/m^3. Respiratory protection with a minimum APF of 10 is specified for that use and, when the use of RPE and exposure duration are taken into account, the RWC exposure estimate is 3 µg Co/m^3.

B.9.6.3. Risk management approaches

An overview of the risk management measures specified for this use in the exposure scenarios is provided in appendix 3 (CoRC, 2018). Reaction processes take place in closed systems, while ‘raw material handling’ may take place in open systems with no engineering controls, according to the exposure scenarios of the registration dossiers. RPE with minimum APF of 10 is specified for the ‘raw material handling’ as described above.

Further information on the conditions of use ‘raw material handling’ was provided by one company in the call for evidence (CfE,comment 512). According to this company, cobalt sulphate is used in this company as an intermediate and supplied for use in the form of an aqueous solution (8% concentration). IBC containers holding cobalt sulphate solution are connected by flexible hoses with a camlock clutch with one-way valve to the production plant. Cobalt sulphate solution is handled in an automated closed system without human intervention to prevent worker exposure. It si to be noted that this company reports that they have substituted the use of cobalt sulphate in powder form for the aqueous solution with a cost of 10 000 euros to 100 000 euros/year. No measurements on the exposure reduction to workers are available.

No further information regarding the conditions of use of the cobalt salts in the manufacture of dyes for the textile industry is available to the Dossier Submitter.

B.9.7. Use as catalysts

B.9.7.1. General information

According to the exposure scenarios of the registration dossiers (CoRC, 2018), cobalt di(acetate) and cobalt sulphate are used as catalysts in the synthesis of chemical compounds. The use of the cobalt salts as catalysts is not an intermediate according to REACH.

Table 23 below presents an overview of the different production stages and the form of the cobalt salts at each stage.

Table 23: Processes involved in the use of the cobalt salts as catalysts (CoRC, 2018)

Exposure Scenario	Tasks	Form of cobalt salt	Cobalt salt content
Use of catalyst	Loading, unloading, reaction, immediate removal of wet splashes	Aqueous solution	Not restricted
Sampling for quality assurance	Sampling	Aqueous solution	Not restricted

B.9.7.2. Worker exposure

Estimates of inhalation exposure and details of risk management measures applied for the use of cobalt salts as catalysts are set out in appendix 3 based on the exposure scenarios of the registration dossiers (CoRC, 2018). It is noted that the maximum concentration levels of cobalt in air [19] (based on personal samplers) for the use of the cobalt salts is 3 µg Co/m^3. The use may take place continuously, resulting in an exposure level of 3 µg Co/m^3 as RWC 8 h TWA.

The CPME (2017) provided some further elaboration on the use of cobalt di(acetate) as a catalyst as part of ECHA's call for evidence. Cobalt di(acetate) is provided for use in sealed containers as a solution, containing cobalt di(acetate) and acetic acid along with two other co-catalysts. The raw material handling phases involves the use of inlet pipework and hose lines to discharge goods into production facilities. No direct manual handling by workers is involved in this stage. According to a trade association (pers. comm., 16/01/18) the salt is consumed in the process. Cobalt will be present in the final goods as cobalt terephthalate (<10ppm by weight) which is insoluble. The process will also generate waste residues which go through a recovery process. Downstream users interviewed indicated that the used catalyst is typically recovered on-site and can be converted back to diacetate form, commonly off-site by an external professional. The trade association (pers. comm., 16/01/18) notes that cobalt di(acetate) remains within aqueous solutions and is not used as a powder at any point in the process.

According to the information provided in the call for evidence (CfE 493), cobalt sulphate is also used as catalyst in one manufacturing step in a production site in the EU. The cobalt sulphate is supplied as aqueous solution, unloaded from drums into a process tank and supplied to the process continuously in a controlled way. No further information regarding the manufacturing process was submitted by the respondent.

B.9.7.3. Risk management approaches

An overview of the risk management measures at each process step of the use of cobalt-containing catalysts using cobalt salts, as indicated by exposure scenarios of the registration dossiers (CoRC, 2018) is provided in appendix 3.

In the exposure scenario of the registration dossiers, the use of cobalt di(acetate) is identified as the 'use of catalyst in a closed system'. However, the level of containment is not fully clear. The exposure scenario describes the process as 'closed' (for process temperatures up to 600 degrees Celsius) or 'semi-closed' for process temperatures up to 160 degrees Celsius). According to the respondents to ECHA survey (two respondents for this sector of use) the use as catalyst takes place in closed systems.

One company (confidential, CfE 498) reports that cobalt di(acetate) is purchased as a dilute solution in water and is transferred through closed piping to the reactor vessel, where the in-situ catalytic species is formed, hence there is no handling of solid raw material at the facility. It is indicated that the sampling for quality assurance step is a semi-contained process. Another company reports in the ECHA's survey that in-line x-ray measurement systems are used to measure concentrations of cobalt in the process and minimise the requirements for sampling. Sampling, according to the exposure scenarios, may take place in an open system with no specific risk management measures in place.

The Dossier Submitter notes the potential variability of the conditions of use for this sector, specifically regarding the level of containment of the process which may result in higher levels of exposure to the cobalt salts. It is not clear whether the exposure estimates presented in the registration dossiers reflect the different conditions of use identified in the exposure scenarios.

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[19] Due to the low number of measurements (n=6), the maximum value is provided instead of the 90th percentile as reasonable worst case estimate.

B.9.8. Surface treatment sector

B.9.8.1. General information

The exposure scenarios of the registration dossiers identify four uses for the cobalt salts in the surface treatment sector, as shown in Table 24 below (CoRC, 2018).

Table 24: Overview of uses for the surface treatment sector (CoRC, 2018)

Number	**Identified use**
1	Formulation of metal surface treatment pre-formulations
2	Passivation processes in surface treatment
3	Passivation processes in surface treatment at large industrial sites with continuous processes
4	Plating processes in surface treatment

Table 25 below provides an overview of the different production stages and the form of cobalt salts used at each stage.

Table 25: Processes involved in the surface treatment sector (CoRC, 2018)

Surface treatment	**Exposure Scenario**	**Form of cobalt salt**	**Cobalt salt content**
Formulation of metal surface treatment pre-formulations	Raw material handling	Solid, powder / dust; aqueous solution	Not restricted
	Formulation of solutions	Aqueous solution	Not restricted
	Filling of solutions	Aqueous solution	5 - 25 %
	Cleaning and maintenance	Solid, powder / dust	Not restricted
Use at industrial site - Passivation processes in surface treatment	Raw material handling (solid input materials)	Solid, powder / dust	Not restricted
	Dissolution of solid raw materials	Aqueous solution	Not restricted
	Raw material handling (exclusively aqueous solutions as input materials)	Aqueous solution	Not restricted
	Passivation	Aqueous solution	1 - 5 %
	Cleaning & Maintenance	Solid, powder / dust	Not restricted
Use at industrial site - Passivation processes in surface treatment at large	Raw material handling (exclusively aqueous solutions as input materials)	Aqueous solution	5 - 25 %

Surface treatment	**Exposure Scenario**	**Form of cobalt salt**	**Cobalt salt content**
industrial sites with continuous processes	Passivation	Aqueous solution	1 - 5 %
Use at industrial site - Plating processes in surface treatment	Raw material handling (solid input materials)	Solid, powder / dust	Not restricted
	Dissolution of solid raw materials	Aqueous solution	Not restricted
	Raw material handling (exclusively aqueous solutions as input materials)	Aqueous solution	Not restricted
	Plating	Aqueous solution	Not restricted
	Manual brush plating	Liquid	1 - 5 %
	Cleaning & Maintenance	Solid, powder / dust	Not restricted

B.9.8.2. Worker exposure

Information on numbers of sites in the EU using cobalt salts in the surface treatment sector has been provided by industry (eftec, 2018a). This is shown in Table 26.

A trade association (ZVO, pers. comm., 15/01/18) indicated in an interview that there are around 20-25 companies undertaking formulation of the cobalt salts and between 600-800 companies in Europe using cobalt salts in the surface treatment sector for passivation and corrosion resistance, with approximately 50% of this use occurring in Germany. Very few companies are understood to use the cobalt salts in electroplating. The data presented by eftec (2018a) suggests a higher value, with the number of sites using cobalt salts in the surface treatment sector estimated as being up to 3 000. It is not clear what the cause of this discrepancy is. It is noted that the ZVO estimation for the number of sites in Europe is an extrapolation from the number of sites estimated in Germany. The (ZVO, pers. Comm., 15/01/18) indicate that the extrapolation may not take into account the number of smaller sites in other countries such as Poland.

Within the EU, it was indicated by the ZVO (ZVO, pers. comm., 15/01/18) that the use of cobalt salts in the surface treatment sector is predominantly located in countries with a large automotive sector, such as Germany, although it is noted that production in Poland and the Czech Republic is growing.

The total volume of the cobalt salts used in the EU in the surface treatment sector is estimated by industry (ZVO, pers. Comm., 15/01/18) and eftec (2018a) to be ~500 tonnes a year. It is noted that the volume of use by individual companies is typically quite small (~50 kg/year). It was indicated that a breakdown of the number of sites/workers using cobalt salts for the different processes (formulation, passivation, plating) was not currently available.

Table 26: Numbers of sites and workers for surface treatment in the EU (eftec, 2018a)

	Estimate	**Mean (range)**
Number of downstream users	3 000	1 500-3 000

	Estimate	Mean (range)
Total volume used	500 tonnes	<1 tonne (<1-70)
Total number of workers exposed	7 400 (9%)	<10 (<10-70)
Total number of workers employed	84 400	30 (10-300)
Note: Figures are rounded to avoid impression of false accuracy		

Consideration of worker exposure to cobalt salts can be divided into handling of solid compounds and handling and use of solutions. It is considered by industry that the main hazard associated with the use of cobalt salts in this sector is during any steps that involve the manual handling of the cobalt salts, especially if these are supplied in the solid/powder form.

Formulators of passivation and electrolytic solutions use the cobalt salts in solid (powder and flakes) form or as highly concentrated solutions to produce passivation and electrolytic formulas (ECHA, 2013a). The ZVO notes that most of the solid forms are supplied and used in form of flakes and granulates, with a change from smaller particle sizes (powder) to larger (flakes, “granulates”) for the ease of handling. Formulation of cobalt salt solutions appears to be highly automated, although manual handling of the cobalt salts in powder form might be expected during some operations (ECHA, 2013a). Other stages of operation – preparation of surface treatment baths, the periodic adjustment of chemicals and routine bath-sampling and analysis, as well as cleaning and maintenance – will also involve direct manual work (ECHA, 2013a). It is also noted that decorative plating may be done manually by hand, but this only represents a very minor use within the sector. Workers might be exposed to dust at the formulation stage if salts in powder form are weighed and added manually to the mixture vessel for batch production (ECHA, 2013a).

In the handling of solutions, the ZVO, and other industry association and facilities indicate that the concentrations are typically 0.1% to 2%, and usually <1%. The ZVO indicate the levels in their processes do not exceed 5%. Concentrations of working solutions up to 20% of cobalt sulphate have been identified in some electroplating activities and the use of cobalt salt solutions (up to 32 %) by brush electroplating has also been identified for the in-situ treatment of pieces that cannot be moved because of their size or characteristics (ECHA, 2013a).

Estimates of inhalation exposure and details of risk management measures applied for the surface treatment sector are set out in appendix 3 based on the exposure scenarios of the registration dossiers (CoRC, 2018). The highest air concentration levels (RWC) are reported for the raw material handling with exposures based on personal samplers estimated at 168 µg Co/m^3. However, when the specified respiratory protection with a minimum APF of 10, and exposure duration are taken into account, the exposure level is reduced to 0.4 µg Co/m^3 (RWC 8h TWA). Exposure levels (RWC 8h TWA) for passivation are estimated to be at 1 µg Co/m^3. The activity of plating presents air concentration levels(RWC) of 14 µg Co/m^3 which results in RWC 8h TWA exposure of 7 µg Co/m^3.It is to be noted that for manual brush plating, exposure estimates are calculated by modelling (MEASE (1.02.01)) resulting in an estimate (RWC 8h TWA) of 8 µg Co/m^3.

The ZVO (CfE 510), indicated that measurable concentrations of cobalt could not be detected in any company that measures its exposure levels. ZVO (2011) reports that regular workplace measurements performed by the technical monitoring services of the Occupational Accident Insurance Associations took place at a number of facilities in a company that uses formulations containing cobalt sulphate for passivating electrochemically-deposited layers of zinc. It was reported that exposure levels between 0.59 µg/m^3 to 1 µg/m^3 were measured at the sites. It was not specified if the levels reported were TWA.

One electroplating company involved in the jewellery and watch making industry (CfE, 513) reported levels of < 0.12 µg Co/m^3 (at the operator level, 8 hours of work) and 0.54 µg Co/m^3 (at 1 cm from the tank). It was not specified if the levels reported were TWA. It was noted that all the electroplating tanks at this facility are equipped with local exhaust ventilation (vapour extraction units in tanks) and standard PPE (chemical gloves, goggles and standard work clothing) are also employed.

One (confidential) company report that an assessment was completed in 2013/14 to measure static air concentrations and concentrations for personal exposure at their facility. This monitoring was completed as part of the original restriction process. The results reportedly highlighted very low concentrations with low risk of exposure.

The ZVO also indicated that one (confidential) company, reportedly using cobalt salts in the passivation process, report a workplace concentration of 0.026 µg/m^3 in 2016. The name of the company was not divulged, and it was not specified if this value was expressed as TWA.

B.9.8.3. Risk management approaches

Cobalt salts in surface treatment applications are used in a wide variety of industrial settings ranging from large scale manufacturing units to metal workshops producing a wide array of metal pieces, therefore conditions of use might vary significantly across the sector (ECHA, 2013). The ZVO (pers. comm., 15/01/18) also notes that the volumes of use across different individual facilities will vary considerably.

A detailed overview of the measures in place at the individual steps of the surface treatment process as identified in the exposure scenarios of the registration dossiers (CoRC, 2018) is provided in appendix 3. It is noted that, according to the exposure scenarios, ‘passivation’ may take place in open systems without LEV at small scale operations while it is identified as a closed semi-automated process with LEV at large industrial sites. On the other hand ‘plating’ takes place in closed fully automated systems with LEV (90% effectiveness). For the ‘formulation’ step, the use of LEV is required. The term ‘semi-automated’ can mean that the processes (e.g. immersion of articles in a solution) is carried out by a crane system, controlled manually by an operator (ZVO, pers. comm., 12/03/18).

While appendix 3 specifies the use of LEV (90% effectiveness) at a number of different stages in surface treatment, ZVO (pers. comm.) indicated that in practice there is little requirement or use of this measure in the sector. It was considered that the potential for exposure during most stages is minimal due to the presence of cobalt salts mainly in aqueous solutions. It was indicated that additional LEV measures could be implemented by individual operators if deemed necessary.

While, according to the exposure scenarios of the registration dossers (CoRC, 2018), exposure to solid forms of cobalt salts does occur during manual handling of raw materials in the surface treatment sector (formulation, passivation and plating), this is considered to be an infrequent occurrence. It is indicated by the Cobalt Institute (CoRC, 2017) that very small amounts (<1 tonne/year) of the powder form are used in this sector.

In practice, as noted by the ZVO (CfE 510) the risk management measures applied in surface treatment facilities will not be in place solely to address exposure to cobalt-containing substances, as these facilities often also use other hazardous substances (e.g. chromium VI).

In a survey conducted by ECHA regarding the implementation of risk management measures in different sector of use of the cobalt salts (see annex G), all respondents from the surface treatment sector (16 companies) identified the use of open baths with LEV as a standard practice for ‘electroplating’. The use of closed systems with LEV in electroplating (specified in the exposure scenarios as stated above) was identified as “not practicable” by the respondents. One formulator of surface treatment formulations responded that no technical measures were in place but the use of RPE (APF 20) was required in all activities involving the use of cobalt salts. As noted for other sectors, the actual conditions of use of the cobalt salts diverge significantly among different users and may not be in line with the requirements identified in the exposure scenarios by the registrants.

The implementation of additional risk management measures do seem to be feasible in the surface treatment sector. According to the ZVO (pers. comm., 12/03/18), where required, individual operators could implement LEV as an additional risk management exposure as a feasible and affordable measure to reduce exposure. However, industry representatives consulted currently consider that there would likely be very little additional gain to be made in terms of exposure reduction from these additional measures in most applications. ZVO also noted that, while for smaller-scale uses (e.g. plating in jewellery and watch making) most of the process is manual, the automation of the processes is possible and could be implemented with relatively low cost intensity. It was not specified to what extent this was already being carried out in the smaller-scale applications in the surface treatment sector.

One company (pers. comm., 14/03/2018) reported that one possible additional measure they did consider was whether they could purchase the cobalt salts in a liquid form to avoid exposure to airborne dusts from the flake form during manual handling. This measure was considered by the company to be feasible from technical and practical perspectives, however there may be issues with additional shipping costs and storage issues. The company provided a rough estimate of a €20 000-30 000 per site per annum increase in costs that would result from implementing this measure. The same company noted that they did not consider a fully closed system to be feasible for their operations, and a redesign of the production facility to allow such a closed system would likely mean the plant would no longer be financially viable. The company estimated it could cost as much as €100 000 per site for the redesign and this was considered an excessive measure given the monitoring suggests very low concentrations of cobalt in air. Exposure data was not provided, however.

B.9.9. Biotechnology (and health) sector

B.9.9.1. General information

The registration dossiers identify the following uses for the cobalt salts in the biotechnology and health sector, as shown in Table 27 below (CoRC, 2018).

Table 27: Overview of uses for the biotechnology and health sector (CoRC, 2018)

Number	**Identified use**
1	Formulation and use of mixtures in biogas production
2	Use in fermentation processes, use in biotech and scientific research and standard analysis
3	Formulation and use of fertilisers and /or feed grade materials

Table 28 below provide for each of the uses an overview of the different production stages and the form of cobalt salts used at each stage.

Table 28: Processes involved in the use of cobalt salts used in biogas production (CoRC, 2018)

Surface treatment	Exposure Scenario	Form of cobalt salt	Cobalt salt content
Formulation of mixtures for use in biogas production	Raw material handling	Solid, powder / dust ; Aqueous solution	Not restricted
	Formulation of solutions	Aqueous solution	Not restricted
	Production of solid formulations	Solid	Not restricted
	Filling of solutions	Aqueous solution	< 1 %
	Packaging of solid formulations	Solid, powder / dust	< 1 %
	Cleaning & Maintenance	Solid, powder / dust	Not restricted
Industrial use in biogas production	Dosing of solid material	Solid	< 1 %
	Dosing of liquid material	Aqueous solution	< 1 %
Professional use in biogas production	Handling of sealed bags	Massive object	Not restricted

Table 29: Processes involved in the use of cobalt salts used in fermentation and biotechnology (CoRC, 2018).

Exposure Scenario	Tasks	Form of cobalt salt	Cobalt salt content
Raw material handling	Loading/unloading, weighing	Solid, powder / dust	Not restricted
Operations in closed systems	Operations in closed systems.	Solid, powder / dust	Not restricted
Handling at laboratory scale	Handling at laboratory scale	Solid, powder / dust	Not restricted
Handling of liquid stock solution	Dissolution in water, mixing, further handling of stock solution, sampling, immediate removal of wet splashes	Aqueous solution	1 - 5 %

Table 30: Processes involved in the use of cobalt salts in fertilisers and/or feed grade materials (CoRC, 2018)

Exposure Scenario	Tasks	Form of cobalt salt	Cobalt salt content
Raw material handling	Interim storage in un-opened container, loading/unloading,	Solid ; Aqueous solution	Not restricted

Exposure Scenario	**Tasks**	**Form of cobalt salt**	**Cobalt salt content**
	immediate removal of wet splashes		
Formulation	Mixing, blending, milling.	Solid ; Aqueous solution	1 - 5 %
Filling	Filling of liquids, immediate removal of wet splashes	Aqueous solution	1 - 5 %
Packaging	Dissolution in water, mixing, further handling of stock solution, sampling, immediate removal of wet splashes	Solid, granulate	< 1 %

B.9.9.2. Worker exposure

Information on numbers of sites/workers for the biotechnology sector have been provided by industry (eftec, 2018a) and are shown in Table 31 below.

Overall, it is estimated there are 113 300 workers employed in the EU related to the use of cobalt salts within the biotechnology sector. Depending on the sector, between 2%-30% are potentially exposed to cobalt salts. In terms of the reported number of sites, the majority are accounted for by the biogas sector, while the animal feed sector accounts for the majority of workers employed and exposed. However, there are gaps in the analysis as, according to industry, it is unclear whether there is sufficient coverage of the complete sector for all the uses.

Table 31: Number of sites and workers for the biotechnology sector (CoRC, 2018)

	Animal feed	**Biogas production**	**Fermentation, biotech processes, health and medicine**
Total number of downstream users	Unknown[1]	Unknown[1]	Unknown[1]
Number of sites	4 400[2]	13 800	Unknown
Total volume used (tonnes/year)	200	130	<<10
Total number of workers exposed (% of total employed)	14 000 (28%)	5 400 (30%)	900 (2%)
Total number of workers employed	50 000	18 200	45 100

Figures have been rounded to the nearest 10 to avoid impression of false accuracy.
Notes:
1) The number of downstream users is too uncertain to be estimated.
2) This figure corresponds to sites where formulation of animal feeds take place. It excludes the final use of animal feed by farmers.

The cobalt salts have an essential use within the biotechnology sector (CoRC, 2017). However, specific uses of each of the cobalt salts vary widely across this sector and, therefore, so do exposure levels. Estimates of exposure levels are provided in the registration dossier (CoRC, 2018) for each of the uses in this sector. A short overview of the exposure estimates is provided under each of the separate use sections below, and the detailed information is included in appendix 3.

Biogas production

Estimates of inhalation exposure and details of risk management measures applied for the biogas sector (formulation, industrial and professional use) are set out in appendix 3, based on the exposure scenarios of the registration dossiers (CoRC, 2018). Air concentration levels at the formulation stage range between 0.5 to 2 µg Co/m^3 (RWC 8h TWA, based on personal sampler measurements) while for 'cleaning and maintenance', measurement values are estimated as 82 µ gCo/m^3. Taking the use of RPE (APF =40) into account and the duration of the activities, the exposure estimates (RWC 8h TWA) result in values ranging from 0.5 µgCo/m^3 for 'raw material handling' to 8 µg Co/m^3 for 'cleaning and maintenance'. The industrial and professional use of the cobalt-containing mixtures result in air concentration levels (RWC) of 0.5 µg Co/m^3 and exposure estimates of 0.02 µg Co/m^3 (RWC 8h TWA). It is to be noted that the use of biogas mixtures by professional workers takes place exclusively in biodegradable bags, i.e. as a solid massive form.

Fermentation and biotechnological processes

Estimates of inhalation exposure and details of risk management measures applied for the fermentation and biotechnological sector are set out in appendix 3 based on the exposure scenarios of the registration dossiers (CoRC, 2018). Air concentration measurements (RWC) based on personal samplers are estimated as 1µg Co/m^3. No respiratory protection is specified (except for the use of cobalt dinitrate). When exposure duration is taken into account, the RWC 8h TWA exposure estimates vary from 0.05 to 0.3 µg Co/m^3, depending on the process. General local ventilation with an estimated effectiveness of 78% is generally required.

One company (CfE 517) note that only a limited number of professional employees are involved in handling cobalt salts (sampler of raw material, R&D technician, quality control operator, media preparation operator) in the IVD sector. Appropriate personal protective equipment is reported to be used and practices are carefully designed to minimise any inhalation by performing manufacturing activities under a closed system and in a liquid form. One respondent described using a small quantity (up to 27g) of crystalline cobalt dichloride weighed out in a powder hood and then dissolved in water together with other trace elements, prior to addition to fermentation media.

Additional evidence collected from one company (CfE 506, who manufacture pharmaceutical, diagnostic, and research-only products in the European Union) on cobalt dichloride states that the handling and weighing processes pose the largest risk to exposure. The substance is handled only by a single employee in solid form for approximately 5 minutes at a time, several times a year. Handling is reported to consist of weighing the solid material and dissolving it in an aqueous solution. The employee uses personal protective equipment and handles the material in a safety workbench or glove box. Only one site reports the use of cobalt dichloride as a solid.

Another stakeholder consulted (pers. comm., 2018) note that the cobalt salts are bought in crystalline/ powder form in 50g pots. A maximum of 26g is weighed out inside a powder hood with ventilation. The operator is reported to wear a lab coat, nitrile gloves and face shield. Inside the powder hood a liquid stock is prepared and then poured into a small fermenter. The fermenter is then pumped into a final stage, which is a closed process. Three to four individuals share this workload of up to 10 weighing batches per year; however, worker exposure via inhalation is unknown due to lack of measured data.

Health and medicines

No specific exposure scenarios for this use are available in the registration dossiers but it is understood that the use and exposure are broadly similar to those scenarios for the fermentation and biotechnological sector discussed above.

One company (pers. comm., 23/01/11) using cobalt dichloride as a ('vital') trace element in the fermentation process for the production of antibiotics for animal health provide details of exposure. Cobalt dichloride is purchased by the company in 25kg sacks and exposure may take place during lab testing, raw material processing or during the reaction fermentation process. Air concentration of cobalt salts and exposure levels have been measured by the company and can be seen in Table 32. Training and full PPE are required at all times, along with the use of a respirator for 'raw material handling' (APF = 40) and for the fermentation process (APF = 20).

Table 32: Confidential company information provided on process and exposure in manufacturing process (pers. comm., 23/01/11)

Activity	**Form of salt and operational conditions**	**Workplace air concentration (µg Co/m^3) (RWC)**	**Worker exposure (µg Co/m^3) (RWC 8h TWA)**
Lab testing	Powder form 1 sample for bath, up to 3 times per year, approx. 4 hours of work	Not measured (considered minor)	Not measured (considered minor)
Raw material processing	Powder form 3-4 times per year , 40 minutes of work	7.6 µg Co/m^3	0.23 µg Co/m^3
Fermentation process	Powder form 2 times per 12 hour shift , 50 minutes	29 µg Co/m^3	5.8 µg Co/m^3

Animal feed

It is understood that the use of cobalt salts in fertilisers does not to take place anymore, and it is not further discussed.

The use of cobalt salts as additives in animal feed is subject to the Regulation EC 1831/2003 on additives for use in animal nutrition, which establishes the requirement of an authorisation for this use. The provisions of the authorisation of the cobalt salts as food additives set up in the Commission implementing regulation (EU) No 131/2014 include a number of measures to reduce the potential exposure of users, including:

- Restriction of the supplementation of feed with cobalt salts to certain animal species (ruminants, horses, rabbits).
- The requirement to include the cobalt salts in the compound feed[20] in the form of premixtures (diluted preparation with a cobalt content usually <1%)
- Obligation to place the compound feed on the market in a non-powder form unless it contains coated granulated cobalt carbonate.

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[20] Compound feeds are defined as animal feed containing supplements.

- Obligation to wear appropriate protective gloves, respiratory and eye protection during handling.
- Limitation of content of cobalt in the complete feed to 0.0001%

According to the sectors association, the bulk of cobalt salts used currently in the feed chain are coated cobalt carbonate which reduces substantially the exposure to cobalt (FEFAC, FEFANA and EMFEMA, CfE 491).

It is to be noted that under REACH the use in animal feed is exempted from the registration requirements and from the duty to communicate information on substances and mixtures down the supply chain. However, estimates of inhalation exposure and details of risk management measures applied for the animal feeds sector are set out in the exposure scenarios of the registration dossiers (CoRC, 2018) and presented in appendix 3. The exposure scenarios correspond to the formulation stage of cobalt-containing preparations and premixtures with a concentration in cobalt below 1%. The highest air concentration levels are reported for use in the 'raw material handling stage', with exposure (RWC) based on personal samplers estimated as 168 µg Co/m^3. Respiratory protection with a minimum APF of 10 is specified for that use and, when the RPE and exposure duration are taken into account, the exposure estimate is 0.7 µg Co/m^3 (RWC 8h TWA). RPE is not specified for other stages in the processes (excluding 'cleaning and maintenance'). For the 'packaging' step, exposure estimates are 2 µg Co/m^3 based on modelled data (MEASE 1.02.01). These values are significantly lower than exposure levels reported for packaging tasks in other sectors (e.g. in manufacturing, where measured air concentration levels are as high as of 808 µg Co/m^{3,} based on personal samplers) as a result of the low concentration of cobalt in the formulations (well below 1%) and the physical form (coated granulates) in which cobalt salts are usually incorporated into the animal feed materials.

The industrial and/or professional use of feed grade formulations is not identified in the exposure scenarios of the registration dossiers and no further information is available regarding exposure to workers. As discussed in section A.2.9.1, farmers purchase compound feed in different forms when containing coated granulated cobalt carbonate, or in a non-powder form when containing other cobalt salts. The concentration of the cobalt salts in the compound feed is well below 0.01%, i.e. below the classification limit, except for certain dietetic feed (usually in the form of bolus, liquid drenches or licking blocks with a cobalt concentration below 0.1%). According to the requirements of the authorisation of the cobalt salts for this use, adequate PPE including RPE and gloves are required for the handling of the compounds. Under the conditions of use described, the Dossier Submitter understands that exposure levels arising from the industrial and/or professional use of feed grade formulations may be significantly low (well below 0.01 µg Co/m^3).

B.9.9.3. Risk management measures

An overview of the risk management measures at each process step of the use of cobalt salts in the biotechnology sector, as indicated by the exposure scenarios of the registration dossiers (CoRC, 2018) is provided in appendix 3.

The risk management measures vary depending of the specific sector of use. In general terms, the use of closed systems and/or LEV (from 78% to 90 % effectiveness) is required for those tasks where the pure solid forms are in use. It is noted that the use of mixtures in non-powdered forms with a concentration of less than 1% by weight of the cobalt salt do not require specific risk management measures in the biogas sector.

On the other hand the use of feed grade materials by the downstream is subject to the authorisation requirements under the Regulation EC 1831/2003 on additives for use in animal nutrition (as discussed above).

In a survey conducted by ECHA in the context of developing this restriction dossier (see annex G), all respondent from the biotechnology sector (10 respondents) identified the use of closed systems and or partially enclosed systems with LEV as representative risk management measures implemented for the use of cobalt salts in powdered form in their sector of use.

B.9.10. Other / bespoke uses

B.9.10.1. Humidity indicators

B.9.10.1.1. General information

According to the evidence gathered from downstream user interviews and the CfE submissions, as well as exposure scenarios from the registration dossiers (CoRC, 2018), cobalt dichloride is the only cobalt salt used in the production of humidity indicators. The specific tasks involved in the manufacture of humidity indicators as presented in the exposure scenarios of the registration dossiers are detailed in Table 33.

Table 33: Processes involved in the production of humidity indicators (CoRC, 2018)

Exposure Scenario	**Tasks**	**Form of cobalt salts**	**Cobalt salt content in preparation**
Handling of liquid raw material	Mixing, loading/unloading, weighing, immediate removal of wet splashes	Aqueous solution	> 25 %
Further processing	Heating, printing of bags, dispensing solution on paper, drying, transfer, dipping of cards into solution, immediate removal of wet splashes	Aqueous solution	5 - 25 %
Handling of humidity indicator cards or spotted bags	Handling of bags, cutting and packaging of cards, assembly of humidity indicator plugs	Massive object	1 - 5 %

B.9.10.1.2. Worker exposure

Information provided by the Cobalt Institute (eftec, 2018a) notes that data on numbers of sites using cobalt salts and the number of workers potentially exposed is not available for this sector due to minimal volume and few companies involved.

According to information provided, a company producing humidity indicator cards for sight glasses (CfE 486) purchases cobalt dichloride in the granulate form, requiring an initial processing step to dissolve in water to produce a solution. It should be noted that this represents a relatively minor use (<10 kg/year) within this sector. It is nevertheless not included within the operational conditions of the exposure scenarios of the registration dossiers (CoRC, 2018) that only consider the use of cobalt dichloride as aqueous solution.

A larger company producing humidity indicator cards for industrial and military applications (CfE 503) purchases and uses cobalt dichloride (as well as cobalt bromide and copper bromide – see section E.2.2.7) in the liquid form, thus avoiding the initial processing step of dissolving the solid form to produce the cobalt dichloride solution. Another company (CfE 486) indicate humidity indicator cards are typically produced in batches, with a shift rotation resulting in one worker being in potential contact with the cobalt dichloride at any one time. Total duration of exposure is estimated to be 0.5 to 4 hours. In the final article, a maximum of 2.5% by weight of cobalt dichloride is present.

In a survey conducted by ECHA regarding the risk management measures in place to control exposure to the cobalt salts (see annex G), on company report the use of cobalt dichloride in powder form to manufacture humidity indicators for mine rescue devices. According to the respondent the cobalt salt is applied to a carrier substrate/gel. However, it is not clear whether the substance is initially formulated into a solution, as previously reported by another company, or directly applied in powder from.

Estimates of inhalation exposure and details of risk management measures applied for the manufacture of humidity indicators are set out in appendix 3 based on the exposure scenarios from the registration dossiers (CoRC, 2018). Air concentration levels (RWC) are estimated to be below 0.2 µg Co/m^3 for each production step. No additional respiratory protection is specified for these steps and, when exposure duration is taken into account, the RWC exposure estimate is from 0.05 to 0.1 µg Co/m^3. As stated above, the use of cobalt dichloride in solid form is not included in the exposure scenarios. According to one company reporting this use, the handling of the cobalt salt takes place within an extraction hood for less than 20 min/day. The use of RPE with a P3 filter is required for this step. Exposure levels for this task are not reported, although exposure levels, based on personal and static samplers, reported for other steps in the process are below 0.1 µg/m^3 (outside RPE).

B.9.10.1.3. Risk management approaches

According to the exposure scenarios of the registration dossiers (CoRC, 2018), neither technical measures nor the use of RPE is required to control exposure to the cobalt salts for this use.

One company (CfE 503) note that purchasing the cobalt dichloride in a liquid form reduces the chemical exposure and that the use of appropriate PPE is mandatory at all stages of the manufacturing process; however the PPE used at this site was not specified. Another company (CfE 498) note that the cutting of sheets is carried out in an enclosed system. The use of mandatory PPE such as nitrile gloves and single use face masks has been confirmed by a number of production facilities in stakeholder interviews and call for evidence submissions. The use of extraction hood protected cabins in manufacturing and drying facilities has also been noted.

B.9.10.2. Water treatment chemicals

B.9.10.2.1. General information

ECHA (2017) indicates that the cobalt salts can be supplied either in solid or in aqueous form to the formulators of water treatment chemicals. According to industry the process takes place in batches. Cobalt salts in powder form are manually weighed and loaded into the blending vessel while bulk liquids are transferred from the storage tanks by pumps (ECHA, 2017).

Water treatment chemicals are placed on the market either as powder formulations or as liquid solutions. The use of powder formulations require a pre-mix step where the product is dissolved into a 1% to 25% solution before it is fed into the system.

Table 24 below provides an overview of the different production steps used in the formulation of water treatment chemicals, as presented in the exposure scenarios of the registration dossiers (CoRC, 2018).

Table 34: Processes involved in the formulation of water treatment chemicals (CoRC, 2018).

Exposure Scenario	**Tasks**	**Form of cobalt salt**	**Cobalt salt content**
Formulation	Opening of containers / dosing mixing dissolution, loading/unloading, weighing, re-packaging, sampling	Solid, powder / dust ; solid, crystal ; aqueous solution	Not restricted
Use of formulation	Use of water treatment chemicals, oxygen scavengers and corrosion inhibitors, immediate removal of wet splashes.	Aqueous solution	Not restricted
Cleaning & Maintenance	Manual cleaning, repair and maintenance operations, removal of residuals from e.g. filters/overspill or as waste	Solid, powder / dust	Not restricted

It is noted that the use of formulations in powder form is not included in the exposure scenarios of the registration dossiers.

B.9.10.2.2. Worker exposure

Information on the number of workers using cobalt salts is not available for this sector due to the minimal volumes and few companies involved (eftec, 2018a). The number of sites in the EU using cobalt salts for the formulation of oxygen scavengers is unspecified (ECHA, 2017).

Estimates of inhalation exposure and details of risk management measures applied for the production of water treatment chemicals are set out in appendix 3 based on the exposure scenarios of the registration dossiers (CoRC, 2018). The highest air concentration levels are reported for the formulation stage, with measurement data (RWC) based on personal samplers as high as 168 µg Co/m^3. Taking the use of RPE (APF=10) and exposure duration into account, the exposure estimate is 17 µg Co/m^3 (RWC 8h TWA) for this task. The use of the formulation results in air concentration levels (RWC) of 4 µg Co/m^3, with a RWC 8h TWA exposure levels of 0.1 µg Co/m^3. Cleaning and maintenance results in exposure estimates (RWC 8h TWA) of 8 µg Co/m^3 when the use of RPE and the duration of the activity is taken into account.

The Dossier Submitter notes that the exposure scenarios only consider the use of water treatment formulations as liquid solutions and not in solid form. It is not clear whether the exposure levels reported in the registration dossiers take into account the pre-mix step required in the use of formulations in powder form.

B.9.10.2.3. Risk management approaches

The exposure scenarios of the registration dossiers (CoRC, 2018) specify the use of LEV with 90% effectiveness and of RPE with a minimum APF of 10 for the formulation stage of cobalt salt-containing water treatment chemicals. The use of RPE (minimum APF 10) is also identified for cleaning and maintenance tasks in this sector (see appendix 3).

The use of the formulations as solutions do not require specific risk management measures, according to the exposure scenarios. However, the conditions of use of the formulations in powder form are not specified. It is understood that downstream users should identify the risk management measures to be applied to ensure that exposure to the cobalt salt is controlled for that specific use not covered in the registration dossiers.

B.9.10.3. Other uses

The exposure scenarios identified in the registration dossiers for the use of the cobalt salts as laboratory reference standards are the same as for the fermentation and biotechnological processes, already discussed in section B.9.7. No specific information is available for this use regarding exposure levels, number of workers potentially exposed and number of sites. For information on risk management measures, please refer to section B.9.7.3 above.

B.10. Risk Characterisation

According to the previous section B.4.5, the cobalt salts are considered genotoxic carcinogens with a non-threshold mode of action. In 2016 RAC agreed on the dose-response relationship for the respiratory fraction of the cobalt salts. As the data available do not allow for the characterisation of the carcinogenicity effect of the non-respirable fraction, the Dossier Submitter has applied the dose-response function derived for the lung cancer effect to characterise all types of cancer (local and systemic) associated with a inhalation exposure to the cobalt salts as a precautionary approach to estimate the excess lifetime cancer risks in workers.

The exposure scenarios from the registration dossiers present the exposure values (RWC 8 h TWA) for the different activities in each sector of use. By calculating the combined exposure for each worker resulting from the different activities they may perform, and applying the dose-response relationship, the individual excess lifetime cancer risk can be derived. However the estimation of combined exposure is not straightforward as the different tasks and activities have different annual frequencies and cannot be simply added. Therefore the Dossier Submitter has estimated the exposure values (RWC LT)[21] for each activity taking the frequency into account and then applied the dose response relationship to determine the excess cancer risk resulting from each of the tasks a worker may perform. An example is provided below for the formulation of feed grade materials.

According to the exposure scenarios of the registration dossiers, the formulation of feed grade materials comprises five different activities which result in worker exposure to the cobalt salts. For each of the activities, the duration, frequency, and exposure levels (RWC 8h TWA) are reported in the exposure scenarios. Note that the duration of the activity is already considered in the calculation of the time weighted averaged exposure levels. In order to take into account the different annual frequencies of the activities, the Dossier Submitter has applied the following formula:

Exposure level (RWC LT) = Exposure level (RWC 8 h TWA) x annual frequency/240 shifts

Since the combination of tasks that each worker may perform is not known, and may vary significantly between sites, exposure levels (RWC LT) are added up until the full annual working time (8 h x 240 days = 1920 hours) is completed. In case the duration and frequency

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[21] RWC LT: Reasonable Worst Case exposure levels weighted by time (8 hours/shift) and frequency (240 shifts/year) of the activity.

of the activities result in exposure times higher than the annual working time, only those activities that can be performed in a work year are taken into account, starting by the activities that give rise to the highest exposure levels.

Table 35 below shows the exposure levels for each of the activities in the formulation of feed grade materials. For each activity, the duration and frequency weighted exposure levels (RWC LT) are determined as shown above. By applying the dose-response relationship to the exposure levels, the excess lifetime cancer risk (ELR) resulting from each activity is estimated. In this case since the duration and frequency of the five activities do not cover the annual working time, it is estimated that the same worker will be exposed to the five exposure scenarios. The individual excess cancer risk for workers in this sector of use is derived by adding up the ELR from each activity, resulting in a total value of 2.3 10^{-4}.

Table 35: Calculation of individual excess lifetime cancer risk for the feed grade materials sector

Activity	**Duration[1] (min)**	**Frequency[1] (no of shifts)**	**Exposure levels[1] µg Co / m^3 (RWC 8h TWA)**	**Exposure levels µg Co / m^3 (RWC LT)**	**ELR**
Raw material handling	20	8	0.70	0.02	2.4E-05
Formulation	21	8	0.93	0.03	3.3E-05
Filling	200	12	0.41	0.02	2.2E-05
Packaging	200	12	2.06	0.10	1.1E-04
Cleaning and maintenance	45	12	0.77	0.04	4.0E-05
Total				0.22	2.3E-04

[1] Exposure values as reported in the exposure scenarios of the registration dossiers (CoRC, 2018)

Following this approach, the individual excess lifetime cancer risk values (ELR) are calculated for each of the sectors of use. The results are shown in Table 36 below.

Table 36: Individual Excess Lifetime Cancer Risk levels (ELR)

Sector / use	**ELR[1]**	**ELR (HPE) [2]**
Manufacture of the cobalt salts	1.0E-02	8.8E-03
Manufacture of chemicals	5.3E-03	4.9E-03
Manufacture of batteries	3.5E-03	9.4E-04
Manufacture of catalysts	9.4E-04	9.4E-04
Manufacture of pigments and dyes	5.2E-03	n.a.
Use as catalyst	3.3E-03	n.a.
Use in surface treatment		
- Formulation of surface treatment solutions	2.9E-04	1.1E-04
- Passivation or anti-corrosion treatment processes	4.5E-03	4.4E-03
- Metal or metal alloy plating	1.2E-02	8.2E-03
Use in biotechnology		

- Formulation and industrial use of mixtures in biogas production	2.7E-03	1.6E-03
- Professional use in biogas production	1.6E-05	n.a.
- Use in fermentation processes, in biotech and scientific research and standard analysis	1.9E-04	9.9E-05
- Formulation and use in feed grade materials	2.3E-04	1.7E-04
Bespoke uses		
- Use in humidity indicator cards, plugs and/or bags with printed spots	6.4E-05	n.a.
- Formulation of water treatment chemicals, oxygen scavengers, corrosion inhibitors	3.5E-03	1.8E-03
- Use of water treatment chemicals, oxygen scavengers, corrosion inhibitors	1.4E-04	-

[1] Individual excess lifetime cancer risk levels based on exposure levels weighted by time and frequency (RWC LT).
[2] Individual excess lifetime cancer risk levels based on exposure levels weighted by time and frequency (RWC LT) resulting exclusively from activities with a high potential for exposure, i.e. involving the use of cobalt salts in solid forms and electroplating (where applicable). Cleaning and maintenance activities are not included.
n.a.: not applicable (the use does not involve the use of cobalt salts in solid forms or electroplating according to the exposure scenarios of the registration dossiers).

The individual excess lifetime cancer risk levels vary from 10^{-5} (humidity indicators, professional use of biogas formulations) to 10^{-2} (manufacture of the cobalt salts, metal or metal alloy plating). For some workers, the cancer risk levels may be an overestimation if they perform only part of the activities that may result in exposure to the cobalt salts. Nevertheless, the cancer risk levels above only consider exposure resulting from the use of one of the cobalt salts. For those sectors where alternate use of different cobalt salts may take place, individual excess lifetime cancer risks may be up to five times higher. All in all , the Dossier Submitter considers that the excess cancer risk levels as presented in Table 36 can be considered as a reasonable worst case estimate of the individual excess lifetime cancer risk for workers in each sector of manufacture and use.

The major contributor to the risk levels are those activities with a high potential for exposure, i.e. handling of cobalt salts in powder form and activities where high energy is applied (temperature and/or electrical currents) such as electroplating. The individual excess lifetime cancer risks resulting from these activities (ELR (HPE)) are shown in Table 36 above. It can be seen that cancer risks arising from these activities are major contributors to the overall risk levels, especially for sectors of use where risk values are above 10^{-3}. There are nevertheless two exceptions, i.e. the manufacture of pigments and dyes, and the use as catalysts. In both sectors, according to the description of the exposure scenarios, the use takes place exclusively in liquid form, and in the case of the latter, in closed systems. It is not fully understood the sources of exposure for these activities where it can be expected that the use of liquid forms and even more, fully closed systems in the case of the use as catalysts, entail lower levels of exposure and therefore lower excess cancer risk values. As part of the stakeholder consultation, a company using cobalt sulphate in the manufacture of pigments reported that they had substituted the use of cobalt sulphate in powder form for aqueous solutions to reduce worker exposure. Unfortunately no measurements on the exposure to workers before and after the substitution were provided.

Excess cancer risk levels as presented in the exposure scenarios

The Dossier Submitter notes that the registrants present a calculation of excess lifetime cancer risks for individual tasks and activities as an appendix to the Chemical Safety Assessments and that it results in values that are up to two orders of magnitude lower than those estimated by the Dossier Submitter. The main differences between the calculation of the excess lifetime cancer risk by the Dossier Submitter and the registrants are explained below.

1. Exposure levels: The registrants take the exposure levels based on typical air concentration measurements (median values) as the starting point for the estimation of the cancer risk levels. The Dossier Submitter has used instead the Reasonable Worst Case exposure values (RWC) [22] from the exposure scenarios of the registration dossiers. Typical exposure values are two to tenfold lower than RWC exposure levels.

2. Respirable fraction: The registrants estimate the excess cancer risks resulting exclusively from the respirable fraction, assuming that one tenth of the airborne particles fall within this range. The Dossier Submitter however has estimated that the ratio between the inhalable fraction and the respirable fraction is two (appendix 2). Additionally, the Dossier Submitter has concluded that the non-respirable fraction may result in local and systemic carcinogenic effects upon absorption into the body and contributes to the cancer burden of workers. Since there is not data enough to characterise the carcinogenicity effect of the non-respirable fraction, the Dossier Submitter has applied the dose-response relationship derived by RAC for the respirable fraction to the inhalable fraction as a precautionary approach. This approach results in cancer risk levels ten times higher than those calculated by the registrants' methodology.

3. Combined exposure: The Dossier Submitter has calculated the individual excess lifetime cancer risks for workers resulting from combined exposure from different activities that they may perform at the worksites. Cancer risks resulting from combined exposure are not provided by the registrants in the registration dossiers.

The Dossier Submitter considers that the excess cancer risks as presented by the registrants significantly underestimate the risk for workers resulting from exposure to cobalt in the manufacture and use of the cobalt salts. The use of the median exposure levels instead of the 90th percentile does not take into account potential higher exposures resulting from the different conditions of use encountered at different workplaces. On the other hand, cancer risks resulting from exposure to the non-respirable fraction of the cobalt salts are not considered by the registrants. Although the Dossier Submitter recognises that the application of the dose-response relationship to the inhalation fraction introduces an uncertainty in the calculation of the excess cancer risk levels, it is considered to provide a more accurate approach to the cancer risk estimation than to quantify the risks based exclusively on the respirable fraction.

The differences between the excess cancer risk values calculated by the registrants and by the Dossier Submitter are illustrated for the feed grade materials sector of use, as an example, in Table 37 below.

Table 37: Comparison of excess lifetime cancer risk calculations between the Dossier Submitter and the registrants for the feed grade materials sector

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[22] In the exposure scenarios, RWC exposure values are generally based on the 90th percentile. For those dataset where the number of measurements is very low (below 6 points), either the 95th percentile or the maximum value are used.

	Dossier submitter			Registrants		
Formulation of feed grade materials	**Exposure levels[a] µg Co/m^3 (RWC 8h TWA)**	**Exposure levels[b] µg Co/m^3 (RWC LT)**	**ELR**	**Exposure levels µg Co/m^3 (Typical 8h TWA)**	**Exposure levels µg Co/m^3 (Typical LT)**	**ELR**
Raw material handling	0.70	0.02	2.4E-05	0.0778	0.0026	2.70E-07
Formulation	0.93	0.03	3.3E-05	0.0398	0.0013	1.40E-07
Filling	0.41	0.02	2.2E-05	0.1720	0.0086	9.03E-07
Packaging	2.06	0.10	1.1E-04	0.8602	0.0430	4.52E-06
Cleaning and maintenance	0.77	0.04	4.0E-05	0.1219	0.0061	6.39E-07
Total	**-**	**0.22**	**2.3E-04**	**-**	**-**	**-**

[a] RWC exposure values as reported in the exposure scenarios from the registration dossiers (CoRC, 2018)
[b] RWC exposure values weighted by time and frequency (8 hour, 240 shifts)

As shown in Table 37 for the formulation of feed grade materials, the approach from the Dossier Submitter results in excess lifetime cancer risk levels two orders of magnitude higher than those estimated by the registrants.

Conclusion on risk characterisation

Based on the Dossier Submitter calculations, the individual excess lifetime cancer risk levels vary from 10^{-5} (humidity indicators, professional use of biogas formulations) to 10^{-2} (manufacture of the cobalt salts, metal or metal alloy plating). In general terms the major contributor to the risk levels are those activities with a high potential for exposure, i.e. handling of cobalt salts in solid form and activities where high energy is applied (temperature and/or electrical currents) such as electroplating, although risk levels above 10^{-3} have been also estimated for sectors of use where the cobalt salts are used as a solution in fully closed systems (use as a catalyst). The Dossier Submitter considers that individual excess cancer risk levels in the range of 10^{-5} to 10^{-2} resulting from exposure to the cobalt salts do not demonstrate that exposure is controlled to a risk level of low concern and should be addressed within the present restriction.

In addition, the Dossier Submitter considers that individual excess lifetime cancer risks in the actual worksites may be considerably higher than those calculated and presented in Table 36, taking into account that downstream users may deviate from the exposure scenarios proposed by the registrants and adopt their own risk management measures to ensure what registrants consider the safe use of the substance, i.e. exposure levels below a DNEL value of 40 µg Co/m^3. It is important to highlight that lifetime exposure levels in the range of 40 µg Co/m^3 result in cancer risk levels of 4 x 10^{-2}.

Annex C: Justification for action on a Union-wide basis

See section 1.3.

Annex D: Baseline

See section 1.4.

Annex E: Impact Assessment

E.1. Risk Management Options

See section 2.2.

E.2. Alternatives

E.2.1. Identification of potential alternative substances and techniques

E.2.1.1. Introduction

This section provides a brief description of alternative substances and techniques already in, or previously considered for use in the various uses covered by this dossier.

As reported by ECHA (2017), industry has indicated that no valid alternatives to the five cobalt salts have been identified for their intended uses and that no feasible alternatives are expected to be found in the near future. However, it is worth noting that in the eftec (2018b) report for the CI/CoRC, replacement of the cobalt salts had been identified as having occurred in some applications, as described below.

One company (CfE 500) report that a research study is ongoing and first preliminary results will be available in 2020.

E.2.1.2. Manufacture of chemicals

No information was obtained/provided by downstream users (e.g. through interviews, call for evidence responses) on alternatives in this sector.[23]

E.2.1.3. Manufacture of batteries

One downstream user, reporting the use of cobalt sulphate and cobalt dinitrate in battery electrode production, indicated that despite the high cost of cobalt, 2 to 4% of cobalt dihydroxide are needed in the composition of the positive active mass containing mainly $Ni(OH)_2$. Therefore, it is considered by them that no viable alternative to the use of cobalt salts is available.

No information was obtained/provided by downstream users (e.g. through interviews, call for evidence responses) on the shortcomings of alternatives or on past research done on alternatives in this sector.

E.2.1.4. Production of catalysts

E.2.1.4.1. Production of hydrotreating/desulphurisation catalysts

In the production of hydrotreating/hydrodesulphurisation catalysts, it is also indicated by industry that there are no suitable alternatives. It was noted that there are continuous R&D efforts to improve catalyst products to prepare and performance-test new possible catalyst

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[23] It should be noted that the scope of the current study has involved consultation with manufacturers and downstream users of the five cobalt salts. For use of the cobalt salts in the chemicals sector, the development of alternatives could be dictated by the users of the cobalt-containing products manufacturer in this sector, where, for example the use of alternatives in their downstream uses could alleviate the use of cobalt salts completely. This aspect is out of the scope of the present study.

production recipes. Through this work an industrially realistic substitute for cobalt has not been found to date.

One catalyst manufacturer (pers. comm., 12/01/18) interviewed indicated that cobalt carbonate is considered the best solution as, unlike other alternatives, it leaves no unwanted trace of counter ions and produces only CO_2. There are no other suitable alternatives according to downstream users interviewed. ECMA (2018) note that for hydrotreating catalysts in oil refining (which represents the main application of cobalt in heterogeneous catalysts), most transition metals can catalyse the process. The ECMA (2018) report identifies nickel-molybdenum (Ni-Mo), iron-molybdenum (Fe–Mo), molybdenum (Mo) and ruthenium (Ru) as potential alternatives.

Industry stakeholders interviewed indicate the main potential alternative to cobalt is nickel. It is considered that Ni-based catalysts are very good hydrodenitrogenation and hydrogenation catalysts, relative to Co-based catalysts but give rise to a relatively high hydrogen consumption, with Co-based catalysts being the superior hydrodesulphurisation catalyst. ECMA (2018) notes that although nickel-molybdenum (NiMo) catalysts are very active in hydroprocessing processes it is highly unlikely that a drop-in replacement alternative to CoMo based on nickel will be possible due to both technical and economic (i.e. associated with refinery redesign) constraints.

Switching from Co-based to Ni-based catalyst is considered possible for only a very limited number of operations because this generally leads to products with higher degrees of hydrogenation and lower octane number. Refiners with lower pressure capabilities may not be able to use Ni-based catalysts, according to their response. Industry also expressed concern that the use of these NI-based alternatives would not allow the current levels of desulphurisation of fuels, as required by European fuel quality legislation.

Eijsbouts *et al* (2013) have reviewed and tested the potential alternatives for alumina supported Co/Ni–Mo/W catalysts in hydrotreating units used in oil refining. However, the number of options is shown to be limited as many alternative compositions are either very expensive or are known to be toxic.

It is reported that several compositions have sufficiently high activities for the process (e.g. those based on Ru, Rh, Os and Ir sulphides), but their feasibility as an alternative is limited because the costs are several orders of magnitude higher than those of a commercial Co–Mo catalyst (Eijsbouts, 2013). For example, ECMA (2018) indicate that ruthenium is the most active hydroprocessing catalyst and attractive from a technical perspective; however, due the very limited availability and the resulting high market prices ruthenium is not regarded as a realistic alternative to CoMo catalysts. Indeed, it is reported by industry that that the cost of Ru catalyst is over 400 times higher and can also lead to unwanted reactions. The metals used in these catalysts may also not be available in sufficient amounts for commercial use. For example, industry noted that ~5 tonnes of Ru is mined globally per year, with the industry requiring ~5000 tonnes if this were to be used as an alternative.

While Fe–Mo/W catalysts are attractive from a health and cost perspective, their activity is reportedly too low for commercial application (Eijsbouts, 2013). ECMA (2018) also indicate that alternatives, iron-molybdenum and molybdenum-based catalysts, have significantly lower desulphurisation activities than CoMo catalysts. It was also noted that Fe–Mo/Al2O$_3$ and Mo/Al_2O_3 catalysts are the only Co- and Ni-free alternative compositions exhibiting appreciable activity, but the activity levels are still substantially lower than those of the Co- and Ni-promoted catalysts (Eijsbouts, 2013). One company reported that a catalyst based on a combination of iron and molybdenum, for instance, can reach at the very best half the activity of the cobalt-molybdenum based systems, resulting in much higher costs.

One company (CfE 516) also describe the alternative catalysts considered in oil refinery processes. A literature review by Toulhoat and Raybaud (2003) is cited, which concluded that catalysts containing iron and molybdenum compounds, zinc and molybdenum compounds, and copper and molybdenum compounds have very low activity compared to catalysts containing cobalt and molybdenum compounds. Catalysts containing nickel and molybdenum instead of cobalt and molybdenum have also been considered but these reportedly suffer from lower stability and faster deactivation compared to cobalt-containing catalysts, resulting in more frequent change-outs and resulting higher costs.

One trade association (CfE 494) consider that, at present, there is no other effective alternative for HDS catalysts applied in the low-pressure desulphurisation processes of middle distillates than the combination of Co / Mo sulphides.

E.2.1.4.2. Production of gas to liquid (GTL) / Fischer-Tropsch catalysts

One trade association (CfE 494) report that the current commercial GTL plants are geared towards the use of cobalt and modification of the plants would be very costly to industry. Iron- and ruthenium-based catalysts have been highlighted as potential alternatives to cobalt salts in this process (ECMA, 2018).

ECMA (2018) note that iron is relatively inexpensive option, and reduces the overall hazard related to the use of a CMR substance, and is suitable for a low hydrogen/carbon monoxide ratio as in coal gasification. However, cobalt is considered more suitable for higher H_2/CO ratios, as in natural gas-based plants, where iron catalysts have significantly shorter lifetimes compared to cobalt-based catalysts (months rather than years). The use of iron would also result in much higher emissions of CO_2 as a significant portion of the oxygen from CO dissociation would be discarded as CO_2 rather than H_2O as is the case with the cobalt salts. Using iron-based catalysts will lead to much higher costs in natural gas-based operations due to reactor modifications to operate at higher pressures required (ECMA, 2018).

It is indicated that ruthenium catalysts have the highest activity, function at the lowest reaction temperatures, and produce the highest molecular weight hydrocarbons (ECMA, 2018). However, there is currently no ruthenium-based solution available for industrial scale use in this sector, mainly due to technical and economic constraints. It is highlighted by industry that ruthenium catalysts are extremely sensitive to poisoning by impurities, reducing the efficiency, as well as being expensive. Furthermore, the global supply is reported as being too scarce to supply this use (ECMA, CfE 505). ECMA (2018) note that, technically it is challenging to use ruthenium-based catalysts because ruthenium(IV) oxide is highly reactive and volatile, meaning ruthenium recycling is difficult, resulting in losses up to 25%.

E.2.1.5. Manufacture of pigments and dyes

No information was obtained/provided by downstream users (e.g. through interviews, call for evidence responses) on alternatives in this sector. However, it is relevant to note that:

- Cobalt pigments make up only a small amount of the total pigments market, and use is primarily of other cobalt compounds (such as the oxides) rather than the five cobalt salts. Indeed, the manufacturers now indicate that it is doubtful that this use actually takes place. No information was identified through downstream user associations contacted in preparation of this report.

- Use of the cobalt salts appears to be almost exclusively as an intermediate i.e. the cobalt salts are not used directly in pigments.

E.2.1.6. Use as catalysts

A trade association (CfE ref 489) indicated that cobalt di(acetate) is used as the only functional catalyst in the industrial production of key polyester monomers and this is considered the global standard technology for production of these polyester monomers by the petrochemical industry. No technically feasible substitute for this use of cobalt acetate currently exists. One downstream user interviewed indicated the global PTA/IPA industry has worked for more than 50 years research on this on the global scale and no viable alternative has ever been found. It is noted that implementation of a viable alternative in this sector is challenging due to the global scale and the high level of competitiveness of this sector.

One company noted that nickel-based catalyst could be used as an alternative to cobalt-based catalysts in the manufacture of acrylic acid from propylene. However, the cobalt catalyst has shown to be 2 to 3% more efficient, which leads to significant energy and raw material savings over the lifetime of the catalyst.

One company (CfE ref 493) note that cobalt hydroxide is a possible alternative to cobalt sulphate as an oxidation catalyst, but that this is hindered by a relatively low solubility in the reaction mixture. Furthermore, the company note that for the reaction to be viable, the cobalt hydroxide would need to be reacted with sulphuric acid, producing cobalt sulphate, resulting in an exposure to workers that can be higher than if cobalt sulphate was used initially. The same company (CfE 493) also note copper oxide (II) as a possible alternative to cobalt sulphate as an oxidation catalyst. However, the quantity required is reported to be several hundred-fold greater than that of the cobalt sulphate catalyst. This has several implications that make the use of Cu_2O unfeasible in this process, including the need for dedicated equipment (such as filters, oxidation reactors) and the generation and subsequent treatment of Cu in waste waters. No other viable has been identified for this process.

One company (pers. comm., 11/01/18) using cobalt di(acetate) in a biorefinery as an oxidation catalyst in the production of bio-based intermediate chemicals from a high oleic-content vegetable oil, indicate that no alternative has been identified that provides an industrially sustainable solution in substitution of the usage of Co salt, but a research study is ongoing and first preliminary results will be available in 2020. It was noted that the only alternative previously considered by industry for this process, that could achieve the same level functionality, is ozone; however, this is not considered for viable due to: (i) environmental/health concerns; (ii) safety concerns related to potential for explosions; (iii) economic impact of high energy consumption.

E.2.1.7. Surface treatment

Cobalt salts themselves are considered by industry stakeholders an alternative to the more hazardous chemicals that have historically been used in the surface treatment sector. In passivation/corrosion resistance, the use of cobalt salts has replaced hexavalent chrome surface treatment applications (CfE 490). Industry considers the use chromium (III) in combination with cobalt dinitrate or cobalt sulphate to be the most viable option to meet customer demand (ZVO, pers.comm, 15/01/18). Cobalt-phosphate plating is also a candidate under evaluation as a replacement for chrome plating. In metal alloy plating, the use of cobalt salts is considered an alternative to gold-cadmium alloys, which are themselves under regulatory scrutiny (ZVO, CfE 510).

In relation to passivation/corrosion resistance, one company (CfE 496) indicate that some cobalt-free passivation processes have already been developed; however long-term experience in the field is not yet available, or not yet representative. Other “parallel technology” solutions e.g. thick layer conversion or use of chromium III without cobalt are possible, but are considered of lower quality so cannot be used for all applications. Zinc layers on steel (the so-called ‘blue passivation’ process) is a widely used alternative already, and is popular due to the lower costs, however this technique gives relatively low corrosion resistance and is not considered suitable for long-term corrosion protection.

Research and development activities have increased in recent years, particularly in the automotive industry where there is strong interest in developing cobalt-free alternatives. For example, essential layer systems "ZnNi transparent" and "ZnNi transparent + sealing” are being considered. However, a number of years will be needed for the required corrosion tests, development of the required optical appearance as well as a validation by field tests (CfE 514).

In relation to metal alloy electroplating, the specific properties required of the alloy will vary depending on the specific application involved; so the feasibility of alternatives will vary. Industry (pers. comm., 15/01/18) currently considers there to be no viable alternatives for cobalt salts in this application as this is the only alloy that will allow the required electrical conductivity and mechanical resistance, where metals like gold and silver are used.

One company (pers. comm., 11/01/18) indicate that a key issue with developing and using alternatives to cobalt salts for the surface treatment applications is ensuring the high-quality requirements of metal components is maintained. For example, it is noted that the level of wear resistance achieved using cobalt salts (e.g. in moving parts of engines) is very high meaning that the longevity, and hence sustainability of products is much greater. In the automotive industry, it is indicated there are no viable alternatives to cobalt salts that meet the required specifications (e.g. light weight, durable). The main issue is reduced corrosion resistance which is crucial for vehicle lifetime and hence for resource efficiency (CfE ref 515).

One company interviewed noted that, while some alternatives are available, it may not be difficult for them to penetrate the market due to specific safety standards in the automotive sector, which require the use of specified chemicals. It can reportedly take a long term for new alternatives to pass the standards and obtain the required qualifications. There is also a cost implication in having the tests for qualification which means companies can be reticent to pay for these as there is no immediate benefit to do so.

One trade association (CfE 510) indicates that the potential alternatives (discussed above) often show drawbacks in corrosion resistance, electrical conductivity, noise emission, contact corrosion, wear resistance, resistance against chemicals and others.

E.2.1.8. Biotechnology (and health) sector

E.2.1.8.1. Animal feeds and fertilisers

All salts of cobalt have the same use/function in feed, that is, as a precursor of vitamin B12 synthesis in the gut flora of certain animal species. According to industry, the salts can substitute each other, but cannot be substituted by any other substance (ECHA, 2013a). There is reportedly no alternative to the supplementation of feed with cobalt for ruminants, horses and animal species with hindgut fermentation (rabbits) as cobalt is an essential component for the synthesis of Vitamin B12 by these animals (CfE 491). An EFSA opinion (2009 and 2012) states that there are not enough data to evaluate the consequences of a potential replacement of cobalt by direct dosing of vitamin B12 on health and performance of animals under field conditions. Such a replacement is also considered inefficient because of the high ruminal degradation rate of oral vitamin B12.

As set out earlier in this report, the manufacturers now consider that formulation and use of fertilisers is no longer a relevant exposure scenario and that these could (subject to confirmation) be removed from the registration dossiers.

Stakeholder evidence (CfE 491) who represent manufacturers of feed additives, premixtures, dietetic feed and compound feed) suggests that no alternatives have been developed by industry as cobalt is an essential element that is deemed irreplaceable. The primary alternative option mentioned by a number of companies is to limit use (through elimination) and minimise worker exposure as much as possible.

E.2.1.8.2. Fermentation and biotechnological processes

No alternative techniques or end-products have been identified by industry and stakeholder respondents for the same reasons as encountered above. Cobalt is an essential element in these biotechnology processes and when absent cell growth and yield is reduced (CfE 517). Where the removal of these salts was attempted, this led to a significantly impaired and adversely affected end-product, and resulted in increased impurities (wca and eftec, 2015b). One company working in the IVD sector stated they are not aware of established alternatives to cobalt dichloride. It is possible that alternative cobalt salts could be used. However, the costs of redeveloping and revalidating the fermentation processes would be likely to exceed €50 000 per fermentation (based on the assessment of one respondent who uses cobalt dichloride in five fermentation processes). This expense is likely to be considered too high for the majority of the fermentations concerned.

One company (CfE 506) reported that when developing new products or processes, the substitution of cobalt salts by alternative substances, such as Vitamin B12, is considered. Substitution is however limited due to technical issues e.g. Cyanocobalamin, the synthetic form of vitamin B12, could lead to discoloration of the final product. This alternative is also more expensive but the key issue is the process to develop the medicinal product and it will require them to be re-registered (with the FDA/EMA) which can be long and expensive. Given that companies have multiple products to reformulate if an alternative is introduced, this is not believed to be a viable alternative.

E.2.1.8.3. Health and medicines

No companies reported on any alternative found to date and no new data was available from stakeholder consultation.

E.2.1.8.4. Biogas production

No companies were available to report on any alternatives found to date.

E.2.1.9. Bespoke uses

E.2.1.9.1. Manufacture of HICs

Cobalt dichloride-free HICs have been developed and are available on the market. [24] It has been demonstrated that HICs free of cobalt dichloride can meet some of the appropriate standards for use such as the accuracy required by international JEDEC standards (Benas, 2010). A completely cobalt-free humidity indicating agent using polystyrene sulphonic acid, organic dye and hygroscopic inorganic salt has also been demonstrated recently (Uryu, 2016). One company (CfE 503) report that HICs using cobalt bromide or copper bromide have been developed as an alternative to using cobalt dichloride, and any possible markets that could change to these alternative products have already done so, resulting in an observed decline in cobalt chloride usage in this sector.

However, it is noted that there are certain industrial and military applications where the chemical cobalt dichloride is integrated in the required specifications and use of cobalt dichloride based products will continue. Other potential alternatives, such as nickel chloride, copper sulphate and copper dichloride have been suggested, but not considered technically equivalent alternatives for the required processes. For example, according to one company

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[24] See https://www.clariant.com/solutions/products/2013/12/09/18/28/humidity-indicator-cards--humidity-indicator-plugs

(CfE 486), there is not considered to be a proven alternative suitable for use in humidity indicators.

One company (pers. comm., 12/01/18) indicate that cobalt dichloride has significant practical advantages over some of these alternatives. The primary reason is due to a much more sensitive range of humidity level creating the desired colour change. An industry stakeholder interviewed noted that the desired colour change is observed for cobalt dichloride over the range 8-12%, while for the alternatives this is observed over the wider range 10-60%. There is also considered by industry to be no alternative to cobalt chloride that can detect high (>60%) humidity levels. For example, there is currently no viable alternative to the 90% RH indicator plug used in locomotive braking systems.

E.2.1.9.2. Water treatment chemicals sector

Although, according to industry, other alternative substances, both organic and inorganic, have been evaluated, none has been found to be as effective as cobalt in the production of oxygen scavengers in water treatment (ECHA, 2017).

E.2.1.9. Laboratory reference standards

No information was available/provided on this subsector through the call for evidence, downstream user interviews or additional evidence.

E.3. Restriction scenario(s)

See report section 2.3.

E.4. Economic impacts

See report section 2.4.

E.5. Human health impacts

See report section 2.5.

E.6. Other impacts

See report section 2.6.

E.7. Practicality and monitorability

See report section 2.6.

E.8. Proportionality (comparison of options)

See report section 2.7.

Annex F: Assumptions, uncertainties and sensitivities

See report section 3.

Annex G: Stakeholder information

Call for evidence for additional information

Between June 2017 and September 2017 ECHA collected additional information via its web site to identify the conditions of use of the five cobalt salts that may give rise to exposure to industrial and professional workers (specifically for those uses identified as intermediates by the REACH registrants), potential alternatives available, and relevant socio-economic information for the preparation of this Annex XV restriction dossier. The background note for the call is available at: https://echa.europa.eu/documents/10162/dace35e4-1ad2-eb7c-0725-146bb480b49f.

In total, around 36 comments were received from individual companies as well as industry and trade associations. The information received has been included to the extent applicable and relevant in this report. For confidentiality reasons, the name of individual companies providing information as part of the call for evidence has not been identified.

Consultation with industry carried out by ECHA's contractor

In order to obtain information on the manufacture and uses of the cobalt salts and the possible impact of their restriction on the industry, a number of European trade organisations and individual companies were contacted during the last quarter of 2017 and the first quarter of 2018. Around 20 interviews with different sectors of manufacture and use of the cobalt salts were carried out as part of the consultation. The consultation was undertaken by ECHA's contractor Woods, which was also responsible for the assessment of the obtained information. The information provided by Woods has been included as part of the restriction report.

Moreover, significant information was made available by the Cobalt Institute (CI) and the European Catalyst Manufacturers Association (ECMA) (for catalysts) in addition to the inputs from interviews and from the call for evidence. This included information on uses of the cobalt salts, numbers of sites/workers, existing and potential future RMMs, exposure values and estimation of excess cancer risk levels. ECHA held a number of meetings with both organisations to follow-up on the data provided. The information has been incorporated where applicable in the restriction report. Where ECHA's view differed from the data submitted, the reasons for the discrepancy are stated in the report.

As a final stage in the consultation with industry, ECHA's contractor launched a web-based survey in April 2018 to gather additional information related to the level of implementation of technical measures to control workers exposure to the cobalt salts. Out of a total of 57 responses, 36 were considered to contain enough information to be further analysed. Respondents represented eight sector of use including manufacture of the cobalt salts, manufacture of chemicals, catalysts, pigments and dyes, surface treatment, biotechnology and humidity indicators. The information provided in the survey is discussed in the report.

The identity of individual companies providing information as part of the consultation with industry is kept confidential throughout the report. Trade organisations are identified with their names where their input is referred to in the report.

Request for information to member states

In February 2018, ECHA requested information to member states on exposure of workers to the cobalt salts and potential substitution activities they may be aware of. The following questions were asked:

a) Typical worker exposure levels resulting from the manufacture and uses of the five cobalt salts.

b) Epidemiological studies (cancer, asthma, skin sensitisation, etc.) related to workers exposed to cobalt-containing substances.

c) Number of cases reported as occupational diseases assigned to cobalt exposure and any available related information (health effect, potential levels of exposure, concomitant exposure to other substances, etc.)

d) Technical risk management measures in place (automation, closed systems, local exhaust ventilation, etc.) to control inhalation and dermal exposure and any information on cost of these measures.

e) Any initiative on substitution related to the uses of cobalt-containing substances.

f) Any regulatory requirements at national and/or regional level such as occupational exposure levels (OELs) for cobalt-containing substances.

Seven member states including Ireland, Germany, Finland, Norway, Sweden, Slovakia and France provided information in response to the request. Their comments and answers have been incorporated in the proposal where applicable and relevant.

Table G: Information submitted by member states in the stakeholder consultation

Member state	Information provided	Restriction Dossier
Ireland	a) Typical worker exposure levels resulting from the manufacture and uses of the five cobalt salts. *No information provided.* b) Epidemiological studies (cancer, asthma, skin sensitisation, etc.) related to workers exposed to cobalt-containing substances. *No information provided.* c) Number of cases reported as occupational diseases assigned to cobalt exposure and any available related information (health effect, potential levels of exposure, concomitant exposure to other substances, etc.) *Information regarding number of cases of skin diseases and asthma in the period 2005 to 2017 provided..* d) Technical risk management measures in place (automation, closed systems, local exhaust ventilation, etc.) to control inhalation and dermal exposure and any information on cost of these measures. *No information provided.* e) Any initiative on substitution related to the uses of cobalt-containing substances. *No information provided.* f) Any regulatory requirements at national and/or regional level such as occupational exposure levels (OELs) for cobalt-containing substances.	a) – b) – c) Number of cases included in section B.4.2. d) – e) – f) Information presented in section B.9.1.2.

	Occupational exposure limit 0.1 mg/m3, Sens	
Germany	a) Typical worker exposure levels resulting from the manufacture and uses of the five cobalt salts. *Several sources of information provided.* b) Epidemiological studies (cancer, asthma, skin sensitisation, etc.) related to workers exposed to cobalt-containing substances. *Several references provided.* c) Number of cases reported as occupational diseases assigned to cobalt exposure and any available related information (health effect, potential levels of exposure, concomitant exposure to other substances, etc.) *No specific information related to cobalt available.* d) Technical risk management measures in place (automation, closed systems, local exhaust ventilation, etc.) to control inhalation and dermal exposure and any information on cost of these measures. *No information provided.* e) Any initiative on substitution related to the uses of cobalt-containing substances. *No information provided.* f) Any regulatory requirements at national and/or regional level such as occupational exposure levels (OELs) for cobalt-containing substances. *In Germany, an exposure risk relation of 5µg Co/m^3 (4:1000, tolerable risk) and 0,5µg/m^3 (4:10000, acceptable*	a) Information from the German Technical Rules (TRGS 561, 2017) related to exposure levels in surface treatment is included in section 1.2.5.2. Other sources of information do not distinguish between exposure to different cobalt compounds cannot be used to estimate exposure to the cobalt salts. b) References already considered in the RAC agreement (ECHA 2016) on which the hazards assessment of the restriction dossier is based. c) – d) – e) - f) Information presented in section B.9.1.2.

	risk) for cobalt metal AND cobalt compounds has been introduced.	
Finland	a) Typical worker exposure levels resulting from the manufacture and uses of the five cobalt salts. *Air monitoring data based on FIOH measurements from 2004-2007 provided (more recent evaluations not available yet).* b) Epidemiological studies (cancer, asthma, skin sensitisation, etc.) related to workers exposed to cobalt-containing substances. *No information provided.* c) Number of cases reported as occupational diseases assigned to cobalt exposure and any available related information (health effect, potential levels of exposure, concomitant exposure to other substances, etc.) *Information regarding number of cases of skin diseases and asthma in the period 2007 to 2014 provided.* d) Technical risk management measures in place (automation, closed systems, local exhaust ventilation, etc.) to control inhalation and dermal exposure and any information on cost of these measures. *No information provided.* e) Any initiative on substitution related to the uses of cobalt-containing substances. *No information provided.*	a) The information do not distinguish between exposures to different cobalt compounds and cannot be used to estimate exposure to the cobalt salts. b) - c) Although Finland submitted information on the number of cases of occupational skin diseases and asthma cases corresponding to the period 2007 to 2013, the data are related to exposure to cobalt and nickel compounds and therefore have not been considered in the dossier. The data from 2014 which relates to exposure to cobalt compounds is included in section B.4.2. d) - e) – f) –

	f) Any regulatory requirements at national and/or regional level such as occupational exposure levels (OELs) for cobalt-containing substances. *No information provided.*	
Norway	a) Typical worker exposure levels resulting from the manufacture and uses of the five cobalt salts. *Data on exposure to cobalt from 1990 to 1997 provided.* b) Epidemiological studies (cancer, asthma, skin sensitisation, etc.) related to workers exposed to cobalt-containing substances. *No information provided.* c) Number of cases reported as occupational diseases assigned to cobalt exposure and any available related information (health effect, potential levels of exposure, concomitant exposure to other substances, etc.) *No information provided.* d) Technical risk management measures in place (automation, closed systems, local exhaust ventilation, etc.) to control inhalation and dermal exposure and any information on cost of these measures. *No information provided.* e) Any initiative on substitution related to the uses of cobalt-containing substances. *No information provided.*	a) The information do not distinguish between exposures to different cobalt compounds and cannot be used to estimate exposure to the cobalt salts b) – c) - d) – e) – f) Information presented in section B.9.1.2

	f) Any regulatory requirements at national and/or regional level such as occupational exposure levels (OELs) for cobalt-containing substances. *The last Norwegian occupational exposure limit (OEL) values were set in 2000. The OEL were then reduced from 0.05 to 0.02 mg/m^3.*	
Sweden	a) Typical worker exposure levels resulting from the manufacture and uses of the five cobalt salts. *Information on average exposure levels to cobalt compounds provided.* b) Epidemiological studies (cancer, asthma, skin sensitisation, etc.) related to workers exposed to cobalt-containing substances. *No information provided.* c) Number of cases reported as occupational diseases assigned to cobalt exposure and any available related information (health effect, potential levels of exposure, concomitant exposure to other substances, etc.) *No information provided.* d) Technical risk management measures in place (automation, closed systems, local exhaust ventilation, etc.) to control inhalation and dermal exposure and any information on cost of these measures. *No information provided.* e) Any initiative on substitution related to the uses of cobalt-containing substances.	a) The information do not distinguish between exposures to different cobalt compounds and cannot be used to estimate exposure to the cobalt salts. b) – c) - d) – e) – f) Information presented in section B.9.1.2.

	No information provided. f) Any regulatory requirements at national and/or regional level such as occupational exposure levels (OELs) for cobalt-containing substances. *In Sweden the national occupational exposure level for cobalt (inhalable dusts, including inorganic compounds) is 0.02 mg/m3.*	
Slovakia	a) Typical worker exposure levels resulting from the manufacture and uses of the five cobalt salts. *Information related to exposure to various cobalt compounds provided.* b) Epidemiological studies (cancer, asthma, skin sensitisation, etc.) related to workers exposed to cobalt-containing substances. *No information provided.* c) Number of cases reported as occupational diseases assigned to cobalt exposure and any available related information (health effect, potential levels of exposure, concomitant exposure to other substances, etc.) *No cases of occupational diseases assigned to cobalt exposure identified in the last 5 years. Identified was only one case of occupational contact dermatitis from metals including cobalt in 2017.* d) Technical risk management measures in place (automation, closed systems, local exhaust ventilation, etc.) to control inhalation and dermal exposure and any information on cost of these measures.	a) Information on exposure to the cobalt salts relates to one specific workplace where cobalt dinitrate is used in passivation: "Measurement of cobalt exposure in a personal respiratory zone was expressed as TWA $<0.004 mg/m^3$". This data is included in section 1.2.5.2 of the restriction dossier. Information provided from other workplaces do not specify the exposure levels to the cobalt salts. b) - c) Number of cases included in section B.4.2 d) Use of general and local ventilation and PPE reported. Information included in section B.9.4. e) – f) Information presented in section B.9.1.2.

	Information regarding RMMs in specific workplaces provided. e) Any initiative on substitution related to the uses of cobalt-containing substances. *No information provided.* f) Any regulatory requirements at national and/or regional level such as occupational exposure levels (OELs) for cobalt-containing substances. *Occupational exposure limit 0.05 mg/m^3, Sens. Biologic limit value.*	
France	a) Typical worker exposure levels resulting from the manufacture and uses of the five cobalt salts. *Database including more than 2000 measurements from 2007 to 2017.* b) Epidemiological studies (cancer, asthma, skin sensitisation, etc.) related to workers exposed to cobalt-containing substances. *No information provided.* c) Number of cases reported as occupational diseases assigned to cobalt exposure and any available related information (health effect, potential levels of exposure, concomitant exposure to other substances, etc.) *No information provided.* d) Technical risk management measures in place (automation, closed systems, local exhaust ventilation, etc.) to control	a) The database do not distinguish between exposures to different cobalt compounds and cannot be used in full to estimate exposure to the cobalt salts. The data related to the use in surface treatment and in feed grade material has been taken into account in the dossier for the validation of the exposure data provided in the registration dossiers (section 1.2.5.2). b) – c) - d) – e) – f) -

	inhalation and dermal exposure and any information on cost of these measures. *No information provided.* e) Any initiative on substitution related to the uses of cobalt-containing substances. *No information provided.* f) Any regulatory requirements at national and/or regional level such as occupational exposure levels (OELs) for cobalt-containing substances. *No information provided.*	

Appendix 1: Calculation of exposure levels (weighted over time and frequency)

This appendix defines the methodology to calculate exposure levels weighted over time and frequency in order to demonstrate whether exposure levels resulting from the implementation of an exposure scenario result in values equal or above the reference exposure value defined in the conditions of the restriction.

Inhalation exposure levels will be determined by workplace measurements of cobalt concentration in air. Procedures for workplace measurements of cobalt concentration in air are presented in Table 38 below. Other analytical methods can be used as long as they fulfil the performance requirements established in EN 482.

Table 38: Measurement procedures for cobalt concentration in air

Standard	**Analytical Technique**	**LOD method** [a]	**LQ method** [b]	**LQ air sample [µg Co/m^3]**
ISO 15202	ICP/AES [1]	2.3 µg Co/L in 25mL sample	7.7 µg Co/L in 25mL sample	0.8[c]
ISO 30011	ICP/MS [2]	0.017 µg Co/L in 25mL sample	0.057 µg Co/L in 25mL sample	0.006[c]
ISO 30011	ICP/MS [3]	0.000 41 µg Co/L in 25mL sample	0.003 µg Co/L in 25mL sample	0.000 3[d]
DGUV Information 213-515.03	GFAAS [4]	n.a.	27.3 µg Co/L in 20 mL sample	1.82[e]
IFA 7808	ICP/MS [5]	n.a	n.a	0.17[e]

a) Limit of Detection of the method as identified in the procedure
b) Limit of Quantification of the method as identified in the procedure
c) Limit of Quantification in an air sample (assuming a sampling time of 2 hours at 2.0 L/min) (Vetter *et al*, 2018)
d) Limit of Quantification in an air sample calculated by the Dossier Submitter (assuming a sampling time of 2 hours at 2.0 L/min)
e) Limit of Quantification in an air sample provided in the procedure (assuming a sampling time of 2 hours at 10.0 L/min)
[1] Inductively Coupled Plasma Atomic Emission Spectrometry
[2] Inductively Coupled Plasma Mass Spectometry – Closed vessel microwave digestion
[3] Inductively Coupled Plasma Mass Spectometry – Open vessel microwave digestion
[4] Graphite Furnace Atomic Absorption Spectrometry –Hot plate acid digestion
[5] Inductively Coupled Plasma Mass Spectometry

Workplace measurements will be carried out following the requirements identified in EN 689. The following specific conditions apply:

1) Measurement conditions will be selected in a way that the measurements results give a representative view of exposure under working conditions.
2) The exposure measured will correspond to the inhalable fraction (according to EN 481).
3) Sampling will take place at least for the duration of the tasks resulting in exposure to the cobalt salts. If the tasks last longer than a working shift, the sampling duration time will cover as a minimum the full working shift.
4) Personal sampling devices should be used when possible attached to the worker's body. As an exception, stationary measuring systems can also be used if the measuring results permit an assessment of the exposure. The sampling must be conducted in the case of stationary measurements on respiration level and in the immediate proximity of the worker. In cases of doubt, the location with the higher risks must be chosen as the

measuring location. The decisions in favour of stationary measurements must be justified in each individual case.

5) Measurements will be performed outside RPE. If RPE is worn by the operators during the sampling time, the corresponding reduction of exposure can be applied to the measurement results.

6) For measurement results with a value of zero, the limit of detection (LOD) of the method will be taken as the result.

The measurement values obtained represent the exposure levels over the sampling time (EL). When more than one sample is available for the same duration time, the exposure value will be represented by the arithmetic mean of the measurements. If there are different sampling times, a time-weighted arithmetic mean will be derived.

For the calculation of the exposure levels weighted over time and frequency (8 hours, 240 shifts) the following formula applies:

$$Exposure\ level\ (weighted\ over\ 8\ hours, 240\ shifts) = EL\ x \frac{d}{8}\ x \frac{f}{240}$$

Where:

EL= *Exposure level (inhalable fraction) (µg Co/m*^{3}*)*

d= *Sampling time (in hours)*

f= *Annual frequency of the activity*

Exposure levels weighted over 8 hours and 240 shifts represent an equivalent daily exposure to the cobalt salts for a working lifetime (40 years).

In case of workers performing several tasks resulting in exposure to the cobalt salts (either daily or annually), exposure levels weighted over time and frequency (8 hours, 240 shifts) will be calculated as the sum of the exposure levels calculated for each of the tasks:

$$Exposure\ level\ (weighted\ over\ 8\ hours, 240\ shifts) = \sum_{i=1}^{n} ELi\ \ x \frac{di}{8}\ x \frac{fi}{240}$$

Where:

ELi= *Exposure level resulting from task i (inhalable fraction) (µg Co/m*^{3}*)*

d_i= *Sampling time of task i (in hours)*

fi= *Annual frequency of task i*

n= *number of tasks a worker performs resulting in exposure to the cobalt salts*

Appendix 2: Extrapolation from inhalable to respirable exposure levels

The exposure values of the cobalt salts presented in the registration dossiers (CoRC, 2018) and available in literature correspond in general to the inhalable fraction[25] (particles smaller than 100 µm). Extrapolation from the inhalable fraction to the respirable fraction[26] is only possible if information on the particle size distribution at the actual workplaces is available. A report provided by the cobalt industry as part of the call for evidence (CoRC,2017) proposes a ratio of 10 of the inhalable fraction to the respirable fraction as a reasonable worst case particle size distribution. The CoRC report builds on the analysis performed in a previous report by Vetter *et al* (2016) based on actual measurements conducted by the IOM (Institute of Occupational Medicine) in 2014 (Spankie and Cherrie, 2014, confidential). The report from industry and the conclusions from the dossier submitter are presented below.

Particle size distribution based on cobalt monitoring as proposed by industry

The Spankie and Cherry report (2014) present the results from the cobalt monitoring carried out at three worksites. The particle size information was obtained by use of eight-stage Marple cascade impactors that were calibrated to sample the inhalable fraction including respirable particles. According to the Spankie and Cherry report, the respirable fraction would comprise the cobalt collected in the first five stages, i.e. below 6 µm.

Based on the data collected by Spankie and Cherry, the particle size distribution for each of the processes is estimated by Vetter *et al* (2016) (see Table 39 and Figure 1 below). According to Vetter *et al*, the respirable fraction would comprise those cobalt particles with a particle size below 3.5 µm. This is in contradiction with the original measurement report, where the cut-off point for the respirable particle size was identified at 6 µm.

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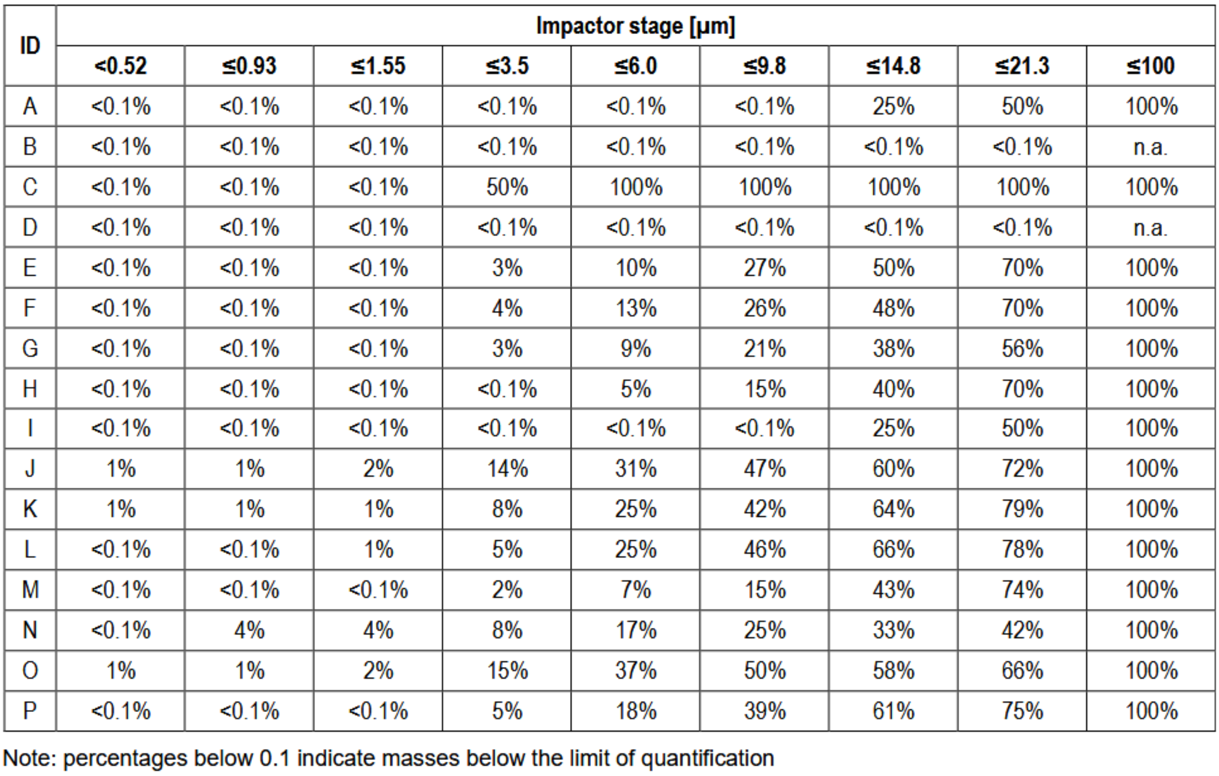
[25] Inhalable fraction: mass fraction of total airbone particles which is inhaled through the nose and mouth (EN 481).

[26] Respirable fraction: mass fraction of inhaled particles penetrating to the unciliated airways (EN 481).

Table 39: Cumulated cobalt percentages (total impacted cobalt mass =100%)



ID	Impactor stage [µm]								
	<0.52	≤0.93	≤1.55	≤3.5	≤6.0	≤9.8	≤14.8	≤21.3	≤100
A	<0.1%	<0.1%	<0.1%	<0.1%	<0.1%	<0.1%	25%	50%	100%
B	<0.1%	<0.1%	<0.1%	<0.1%	<0.1%	<0.1%	<0.1%	<0.1%	n.a.
C	<0.1%	<0.1%	<0.1%	50%	100%	100%	100%	100%	100%
D	<0.1%	<0.1%	<0.1%	<0.1%	<0.1%	<0.1%	<0.1%	<0.1%	n.a.
E	<0.1%	<0.1%	<0.1%	3%	10%	27%	50%	70%	100%
F	<0.1%	<0.1%	<0.1%	4%	13%	26%	48%	70%	100%
G	<0.1%	<0.1%	<0.1%	3%	9%	21%	38%	56%	100%
H	<0.1%	<0.1%	<0.1%	<0.1%	5%	15%	40%	70%	100%
I	<0.1%	<0.1%	<0.1%	<0.1%	<0.1%	<0.1%	25%	50%	100%
J	1%	1%	2%	14%	31%	47%	60%	72%	100%
K	1%	1%	1%	8%	25%	42%	64%	79%	100%
L	<0.1%	<0.1%	1%	5%	25%	46%	66%	78%	100%
M	<0.1%	<0.1%	<0.1%	2%	7%	15%	43%	74%	100%
N	<0.1%	4%	4%	8%	17%	25%	33%	42%	100%
O	1%	1%	2%	15%	37%	50%	58%	66%	100%
P	<0.1%	<0.1%	<0.1%	5%	18%	39%	61%	75%	100%

Note: percentages below 0.1 indicate masses below the limit of quantification

(Source: Vetter *et al,* 2016)

Cobalt masses could not be fully quantified for samples A to D and for sample I; thus these samples were not further used in the assessment. It is to be highlighted that samples A to D correspond to the measurements performed at one of the worksites and therefore the assessment performed is based on the measurements from only two workplaces: workplace 1 (samples E to H) where processing of cobalt massives takes place and worksite 2 (samples J to P) involved in the production and handling of cobalt powders.

Figure x below shows particle size distributions fitted to cumulated mass fractions as reported by Vetter *et al* (2016).

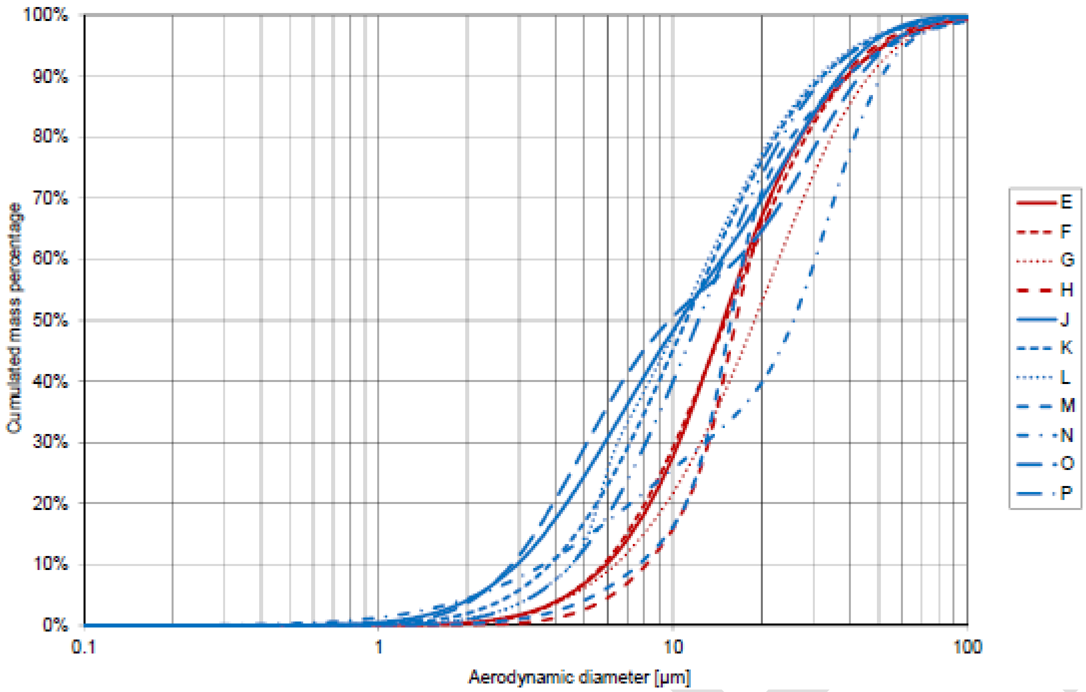


Figure 1: Particle size distributions (PSDs) (Source: Vetter *et al*, 2016)

Based on the particle size distribution values parameterised by Vetter *et al* (2016) (see Table 39 and Figure 1 above), CoRC (2017) report estimates the ratio of inhalable (R_{IvsR}) to respirable fraction. The results are shown in Table 40 below.

Table 40: Ratio of inhalable to respirable fraction

ID	Parameters of $PDF_{inhalable}$					AUC $PDF_{inhalable}$	AUC $PDF_{respirable}$	R_{IvsR}
	p	MMAD 1 [µm]	GSD 1	MMAD 2 [µm]	GSD 2			
E	0.2	14	1.4	15.2	2.2	0.99	0.055	18.0
F	na	15.1	2.1	na	na	0.99	0.059	16.9
G	0.4	11.5	2.2	24.9	1.8	0.99	0.050	19.8
H	0.2	15.5	1.2	17.5	2	1.00	0.027	36.4
Processing of cobalt massives								22.8
J	0.7	6.6	2.2	28.4	1.6	1.00	0.198	5.1
K	na	11.1	2.3	na	na	1.00	0.135	7.4
L	0.1	5.6	1.1	11.9	2.2	1.00	0.120	8.3
M	0.4	15.2	1.2	17.3	2.3	0.99	0.035	28.2
N	0.5	9.5	3.2	34.3	1.4	0.99	0.118	8.3
O	0.6	4.9	1.8	30.2	1.6	1.00	0.230	4.3
P	na	12.2	2.2	na	na	1.00	0.104	9.5
Handling of cobalt powders								**10.2**
All workplaces								14.7

(Source: CoRC 2017)

Where:

PDF is the probability desity function

MMAD is the Mass Median Aerodynamic Diameter

AUC is the area under the curve
GSD is the geometic standard deviation
p is the probability (frequency) density function

CoRC (2017) concluded that, for the handling of the cobalt salts, the average R_{ivsR} of 10 (10% of respirable particles) for the handling cobalt powders could be considered a reasonable worst-case particle size distribution for actual workplaces.

Discussion and conclusion from the Dossier Submitter

Table 40 above presents the arithmetic average R_{IvsR} of 10 as the reasonable worst case ratio of inhalable to respirable fraction for the handling of cobalt powders in actual workplaces. According to industry, this value reflects the respirable fraction related to the handling of cobalt salts on a conservative basis. However, the Dossier Submitter notes that the 90th percentile of the data set is commonly accepted as representing an estimate for the ‘reasonable worst-case’ exposure level and therefore should be used instead of the arithmetic average to characterise the respirable fraction.

In addition, the Dossier Submitter notes that the measurements used in the assessment correspond exclusively to two workplaces and that even within each workplace the variation of the data is significantly high. In the case of the handling of cobalt powders, the ratio of inhalable to respirable fraction varies from a R_{IvsR} value of 4.3 (23.2 % of respirable particles) to 28.2 (3.5% of respirable particles) for the same process and workplace.

Finally, the original measurements do not correspond to the sampling convention for the respirable fraction (cut-off point of 4.25 µm). Assuming a cut-off point of 3.5 µm as proposed by Vetter *et al* (2016) results in a significant underestimation of the respirable fraction. From a general overview of Table 39, it can be seen that the percentage of respirable particles with a particle size below 6 µm (as assumed by Spankie and Cherrie) can be up to 5 times higher than the percentage with a particle size below 3.5 (as assumed by Vetter *et al*).

All in all, the Dossier Submitter considers that the ratio of inhaled to respirable fraction of 10 (10% of respirable particles) proposed by industry significantly underestimates the respirable fraction of the airborne cobalt particles.

The Dossier Submitter notes that regulators often assume a ratio of the inhalable to the respirable particles (R_{IvsR}) of approximately 2 to 4 (i.e. 50% to 25% respirable particles) when they set occupational exposure limits for dusts, including metals. For example:

- SCOEL recommendation for an occupational exposure limit for nickel and inorganic nickel compounds of 10 µg/m^3 and 5 µg/m^3 for the inhalable and respirable fraction, respectively (SCOEL/SUM/85).
- SCOEL recommendation for an occupational exposure limit for manganese and inorganic manganese compounds of 200 µg/m^3 and 50 µg/m^3 for the inhalable and respirable fraction, respectively (SCOEL/SUM/127).
- UK HSE workplace exposure limit for aluminium metals and oxides of 10 mg/m^3 and 4 mg/m^3 for the inhalable and respirable fraction, respectively (EH40/2005).
- UK HSE workplace exposure limit for amorphous silica of 6 mg/m^3 and 2.4 mg/m^3 for the inhalable and respirable fraction, respectively (EH40/2005).

This is in line with the findings in Okamato’s study who investigated over 1600 dust workshops in Japan (Okamoto *et al*, 1998). According to this study, ’’*there is a substantial variation in the respirable to inhalable ratio depending on the type of work and, probably, also on the work conditions*.’’ of different worksites. Statistical analysis of the data shows that the R_{IvsR}

ratio at these workplaces may be in the range of 2 to 5, i.e. 50% to 20% of the inhalable particles are respirable (Okamoto *et al*, 1998).

Based on Okamoto's findings and previous regulatory assessments, the Dossier Submitter estimates that a ratio of 2 (50% of respirable particles) could be used as a worst case estimate to extrapolate the respiratory fraction from the inhalable fraction.

Appendix 3: Data on exposure and risk management measures from the exposure scenarios

In this appendix, information is presented on exposure to cobalt salts and risk management measures for the manufacture and different uses covered in this restriction dossier. The data are derived from the exposure scenarios in the registration dossiers (CoRC, 2018). According to the information provided in the registration dossiers:

- The inhalation exposure levels reported correspond in general to RWC exposure values (Reasonable Worst Case, based on the 90th percentile value). Exposure values are mainly derived from cobalt air concentration measurements with personal samplers.
- For some exposure scenarios for which the number of measurements available is low (counts <6), the RWC is based on the 95th percentile or on the maximum exposure value.
- For some of the exposure scenarios, for which specific monitoring data were not available, analogous data from other cobalt compounds and or activities, have been used to estimate exposure.
- A number of exposure values are derived from modelling (MEASE (1.02.01)). (These values are identified in the tables below).
- All data presented correspond to the inhalable fraction.

For those cases where different exposure values are available for the different cobalt salts, the highest exposure value is presented here.

The methodology used by the registrants for the occupational exposure assessment to the cobalt salts is described in detail in Vetter *et al* (2018 b).

Manufacture of the cobalt salts

Stage	Form of substance	Duration (min)	Frequency (no of shifts per year)	Inhalation exposure			Risk Management Measures[1]			
				No of data points/standard deviation	RWC (µg Co/m^3) (Air concentration data)	RWC 8h TWA(µg Co/m^3) (incl. weighting for RPE and exposure duration)	Contained	Automated	LEV	RPE
Raw material handling[2]	Solid, powder / dust ; Aqueous solution ; Massive object	180	68	26/4.23	206	7.7	no	no	no	APF = 10 90% effectiveness
Preparation of raw material[2]	Aqueous solution	148	178	135/3.18	12	3.7	yes	no	90% effectiveness	no
Reaction[2,4]	Aqueous solution	220	127	94/2.65	5	0.8	yes[3]	no	no	no
Wet process	Aqueous solution	120	122	68/3.72	29	0.7	yes[2]	semi	90% effectiveness	APF = 10 90% effectiveness

Stage	Form of substance	Duration (min)	Frequency (no of shifts per year)	Inhalation exposure			Risk Management Measures[1]			
				No of data points/standard deviation	RWC (µg Co/m^3) (Air concentration data)	RWC 8h TWA(µg Co/m^3) (incl. weighting for RPE and exposure duration)	Contained	Automated	LEV	RPE
Hot process	Solid; Aqueous solution	53	51	25/3.67	181	2.0	yes	no	86% effectiveness	APF = 10 90% effectiveness
Further processing	Solid, powder/dust; Aqueous solution	295	124	75/5.43	239	7.3	yes	no	90% effectiveness	APF = 20 95% effectiveness
Filling of liquids / solutions	Aqueous solution	30	80	-	-	0.3 (MEASE)	no	no	no	no
Filling of liquids/solutions in closed system	Aqueous solution	15	240	-	-	0.02 (MEASE)	yes	no	no	no
Packaging of low and/or medium dusty materials[4]	Solid, pellet / pastille	172	20	30/3.45	141	5.0	no	semi	90% effectiveness	APF = 10 90% effectiveness

Stage	Form of substance	Duration (min)	Frequency (no of shifts per year)	Inhalation exposure			Risk Management Measures[1]			
				No of data points/standard deviation	RWC (µg Co/m^3) (Air concentration data)	RWC 8h TWA(µg Co/m^3) (incl. weighting for RPE and exposure duration)	Contained	Automated	LEV	RPE
Handling of powders with moderate dustiness potential	Solid, powder / dust	139	94	132/4.62	168	4.9	no	no	90% effectiveness	APF = 10 90% effectiveness
Handling of powders with high dustiness potential	Solid, powder / dust	139	94	85/5.86	808	5.9	no	no	90% effectiveness	APF = 40 97.5% effectiveness
Cleaning and maintenance	Solid, powder / dust	94	122	106/4.23	82	1.6	no	no	no	APF = 10 90% effectiveness

[1] **Other Risk Management Measures (incl. PPE)**

- General good occupational hygiene practices
- Gloves
- Certified safety clothing and shoes
- Chemical protective suit
- Eye protection
- Good general ventilation
- Regular training in workplace hygiene practice and proper use of PPE

[2] Exposure to cobalt raw material [3]Closed transfer systems, closed reactor and vacuum scrubbing system [4] Cobalt diacetate only

Manufacture of chemicals (intermediate use)

Use	Stage	Form of substance	Duration (min)	Frequency (no of shifts per year)	Inhalation exposure			Risk Management Measures[1]			
					No of data points/standard deviation	RWC (μg Co/m^3) (Air concentration data)	RWC 8h TWA(μg Co/m^3) (incl. weighting for RPE and exposure duration)	Contained	Automated	LEV	RPE
Manufacture of chemicals	Raw material handling	Solid, crystal / aqueous solution	150	82	132/4.62	168 (analogous data)	5.3	no	no	90% effectiveness	APF = 10 90% effectiveness
	Mixing/Reaction in vessel/batch	Aqueous solution	15	80	94/2.7	5 (analogous data)	0.1	yes	no	no	no
	Hot process[2]	Solid / aqueous solution	10	240	25/3.67	181	0.4	yes	no	86% effectiveness	APF = 10 90% effectiveness
	Cleaning and maintenance	Solid, powder / dust	18	78	106/4.23	82 (analogous data)	0.3	no	no	no	APF = 10 90% effectiveness

Use	Stage	Form of substance	Duration (min)	Frequency (no of shifts per year)	Inhalation exposure			Risk Management Measures[1]			
					No of data points/standard deviation	RWC (μg Co/m^3) (Air concentration data)	RWC 8h TWA(μg Co/m^3) (incl. weighting for RPE and exposure duration)	Contained	Automated	LEV	RPE
Manufacture of carboxylates and resonates	Raw material handling	Solid, powder / dust / aqueous solution	480	110	26/4.2	206	10.3	no	no	90% effectiveness	APF = 20 95% effectiveness
	Raw material handling (exclusively aqueous solutions as input material)[3]	Aqueous solution (5-25%)	20	230	9/1.9	4 (analogous data)	0.2	yes	no	no	no
	Reaction	Aqueous solution	480	240	94/2.7	2	2	yes[4]	no	no	no
	Cleaning and maintenance	Solid, powder / dust	480	48	1	96 (max)	4.8	no	no	no	APF = 20 95% effectiveness

Use	**Stage**	**Form of substance**	**Duration (min)**	**Frequency (no of shifts per year)**	**Inhalation exposure**			**Risk Management Measures**[1]			
					No of data points/standard deviation	**RWC (µg Co/m^3)** **(Air concentration data)**	**RWC 8h TWA(µg Co/m^3)** **(incl. weighting for RPE and exposure duration)**	**Contained**	**Automated**	**LEV**	**RPE**
[1] **Other Risk Management Measures (incl. PPE)** - General good occupational hygiene practices - Gloves - Certified safety clothing and shoes - Chemical protective suit - Eye protection - Good general ventilation - Regular training in workplace hygiene practice and proper use of PPE											

[2] Cobalt sulphate only, [3] Cobalt dichloride only,[4] Closed transfer systems, closed reactor and vacuum scrubbing system

Manufacture of batteries (intermediate use)

Stage	Form of substance	Duration per shift (min)	Frequency (no of shifts per year)	Inhalation exposure (µg Co/m³)			Risk Management Measures[1]			
				No of data points/standard deviation	RWC (µg Co/m³) (Air concentration data)	RWC 8h TWA(µg Co/m³) (incl. weighting for RPE and exposure duration)	Contained	Automated	LEV	RPE
Raw material handling	Solid, powder / dust / Aqueous solution	30	225	55/6.3	153 (analogous data)	1.0	no	no	no	APF = 10 90% effectiveness
Mix preparation	Aqueous solution	160	225	68/3.7	29 (analogous data)	0.95	yes	semi	90% effectiveness	no
Cleaning and maintenance	Solid, powder / dust	40	225	85/5.9	808 (analogous data)	1.7	no	no	no	APF =40 97.5% effectiveness

[1] **Other Risk Management Measures (incl. PPE)**

- General good occupational hygiene practices
- Gloves
- Certified safety clothing and shoes
- Chemical protective suit
- Eye protection
- Good general ventilation
- Regular training in workplace hygiene practice and proper use of PPE

Manufacture of catalysts (intermediate use)

Stage	Form of substance	Duration (min)	Frequency (no of shifts per year)	Inhalation exposure			Risk Management Measures[1]			
				No of data points/standard deviation	RWC (µg Co/m^3) (Air concentration data)	RWC 8h TWA(µg Co/m^3) (incl. weighting for RPE and exposure duration)	Contained	Automated	LEV	RPE
Delivery and storage of raw material	Solid, powder / dust	66	51	27/2.2	2.9	0.4	Predominantly[1]	no	no	no
Dissolution of raw material	Solid, powder / dust, forming aqueous solutions	66	37	6/3	5.7 (95th percentile)	0.7	yes[2]	no	no	yes
Impregnation and drying of raw material on carrier	Aqueous solution, forming non-dusty solids (impregnated supports)	10	6	4/2.2	10.4 (max)	0.2	semi[3]	no	no	no
Filtration and drying of precipitate	Wet filter cake; Slurry; Non-dusty solids	155	31	4/2.2	10.4 (max)	3.4	semi[4]	no	no	no

Stage	Form of substance	Duration (min)	Frequency (no of shifts per year)	Inhalation exposure			Risk Management Measures[1]			
				No of data points/standard deviation	RWC (µg Co/m^3) (Air concentration data)	RWC 8h TWA(µg Co/m^3) (incl. weighting for RPE and exposure duration)	Contained	Automated	LEV	RPE
Calcination of precipitate/supports, or impregnated on support	Wet filter cake; Non-dusty solids	15	45	8/2.4	21.3 (95th percentile) (analogous data)	0.03	semi[5]	no	no	APF = 20 95% effectiveness
Reduction of precipitate	Extrudates (Non-dusty solid)	60	32	8/2.4	21.3 (95th percentile) (analogous data)	2.7	yes	yes	90% effectiveness	no
Cleaning and maintenance	Solid, powder / dust	120	48	26/4.3	97.9	1.2	no	no	no	APF = 20 95% effectiveness

[1] **Other Risk Management Measures (incl. PPE)**

- General good occupational hygiene practices
- Gloves
- Certified safety clothing and shoes
- Chemical protective suit
- Eye protection
- Good general ventilation
- Regular training in workplace hygiene practice and proper use of PPE

[1] Occasionally open process with generic local exhaust ventilation; [2] Closed process with occasional opening. Addition of reagents and dissolution in a closed process, semi-closed sampling; [3] Addition of reagents, impregnation and drying are closed processes. Transfer can be closed or semi-closed process; [4] Closed drying; [5] Closed furnace; Semi-closed transfers.

Manufacture of pigments and dyes (intermediate use)

Stage	**Form of substance**	**Duration (min)**	**Frequency (no of shifts per year)**	**Inhalation exposure**			**Risk Management Measures**[1]			
				No of data points/standard deviation	**RWC (μg Co/m^3) (Air concentration data)**	**RWC 8h TWA(μg Co/m^3) (incl. weighting for RPE and exposure duration)**	**Contained**	**Automated**	**LEV**	**RPE**
Raw material handling	Aqueous solution	60	240	68/3.7	29 (analogous data)	0.4	no	no	no	APF = 10 90% effectiveness
Reaction / Formulation	Aqueous solution	295	240	94/2.65	5 (analogous data)	3.1	yes	no	no	no

[1] Other Risk Management Measures (incl. PPE)

- General good occupational hygiene practices
- Gloves
- Certified safety clothing and shoes
- Chemical protective suit
- Eye protection
- Good general ventilation
- Regular training in workplace hygiene practice and proper use of PPE

[2]Closed pipe system, closed reaction vessels; [3]Closed furnace or well extracted open induction furnace; [4] Reaction in the manufacture of dyes: closed process

Use as catalysts

Stage	Form of substance	Duration (min)	Frequency (no of shifts per year)	Inhalation exposure			Risk Management Measures[1]			
				No of data points/standard deviation	RWC (µg Co/m³) (Air concentration data)	RWC 8h TWA(µg Co/m³) (incl. weighting for RPE and exposure duration)	Contained	Automated	LEV	RPE
Use of catalyst	Aqueous solution	480	240	6/5.45	3.1 (max)	3.1	yes[2]	no	no	no
Sampling for quality assurance	Aqueous solution	5	240	-	-	0.03 (MEASE)	no	no	no	no

[1] **Other Risk Management Measures (incl. PPE)**

- General good occupational hygiene practices
- Gloves
- Certified safety clothing and shoes
- Chemical protective suit
- Eye protection
- Good general ventilation
- Regular training in workplace hygiene practice and proper use of PPE

[2] Closed/semi-closed

Use in surface treatment

Use	Stage	Form of substance	Duration (min)	Frequency (no of shifts per year)	Inhalation exposure			Risk Management Measures[1]			
					No of data points/standard deviation	RWC ($\mu g\ Co/m^3$) (Air concentration data)	RWC 8h TWA($\mu g\ Co/m^3$) (incl. weighting for RPE and exposure duration)	Contained	Automated	LEV	RPE
Formulation of metal surface treatment pre-formulations	Raw material handling	Solid, powder / dust ; aqueous solution	19	35	1	0.2 (max)	0.01	no	no	90% effectiveness	no
	Formulation of solutions	Aqueous solution	75	38	9/1.9	4	0.7	yes	no	90% effectiveness	no
	Filling of solutions	Aqueous solution (5 - 25 %)	61	35	9/1.9	4 (analogous data)	0.5	no	no	no	no

Use	Stage	Form of substance	Duration (min)	Frequency (no of shifts per year)	Inhalation exposure			Risk Management Measures[1]			
					No of data points/standard deviation	RWC (µg Co/m³) (Air concentration data)	RWC 8h TWA(µg Co/m³) (incl. weighting for RPE and exposure duration)	Contained	Automated	LEV	RPE
	Cleaning and maintenance	Solid, powder / dust	33	27	2/3.43	12 (max)	0.8	no	no	no	no
Passivation processes in surface treatment	Raw material handling (solid input material)	Solid, powder / dust	10	4	1	0.2 (max)	0.004	no	no	90% effectiveness	no
	Dissolution of solid raw materials	Aqueous solution	480	240	9/1.9	4	4	no	no	90% effectiveness	no
	Raw material handling (exclusively aqueous solutions as input material)	Aqueous solution (5 - 25 %)	120	240	9/1.9	4	1	no	no	no	no

Use	Stage	Form of substance	Duration (min)	Frequency (no of shifts per year)	Inhalation exposure			Risk Management Measures[1]			
					No of data points/standard deviation	RWC (µg Co/m^3) (Air concentration data)	RWC 8h TWA(µg Co/m^3) (incl. weighting for RPE and exposure duration)	Contained	Automated	LEV	RPE
	Passivation	Aqueous solution (1 - 5 %)	35	240	-	-	0.1 (MEASE)	no	no	no	no
	Cleaning & Maintenance	Solid, powder / dust	240	2	2/3.43	12	6	no	no	no	no
Passivation processes in surface treatment at large industrial sites **with continuous processes**	Raw material handling (exclusively aqueous solutions as input material)	Aqueous solution (5 - 25 %)	15	12	9/1.9	4 (analogous data)	0.1	no	fully	no	no
	Passivation	Aqueous solution (1 - 5 %)	15	240	-	-	0.02 (MEASE)	yes	fully	90% effectiveness	no

Use	Stage	Form of substance	Duration (min)	Frequency (no of shifts per year)	Inhalation exposure			Risk Management Measures[1]			
					No of data points/standard deviation	RWC (µg Co/m^3) (Air concentration data)	RWC 8h TWA(µg Co/m^3) (incl. weighting for RPE and exposure duration)	Contained	Automated	LEV	RPE
Plating processes in surface treatment	Raw material handling (solid input material)	Solid, powder / dust	10	4	132/4.62	168	0.4	no	no	90% effectiveness	APF = 10 90% effectiveness
	Dissolution of solid raw materials	Aqueous solution	60	4	9/1.9	4	0.5	yes[2]	semi	90% effectiveness	no
	Raw material handling (exclusively aqueous solutions as input material)	Aqueous solution	33	195	9/1.9	4	0.3	no	no	no	no
	Plating	Aqueous solution	240	240	2/2.38	14 (max)	7	yes[2]	semi	90% effectiveness	no

Use	Stage	Form of substance	Duration (min)	Frequency (no of shifts per year)	Inhalation exposure			Risk Management Measures[1]			
					No of data points/standard deviation	RWC (µg Co/m^3) (Air concentration data)	RWC 8h TWA(µg Co/m^3) (incl. weighting for RPE and exposure duration)	Contained	Automated	LEV	RPE
	Manual brush plating	Liquid (1 - 5 %)	360	24	-	-	8 (MEASE)	no	no	78% effectiveness	APF = 20 95% effectiveness
	Cleaning & Maintenance	Solid, powder / dust	240	121	2/3.4	12 (max)	6	no	no	no	no

Other Risk Management Measures (incl. PPE)

- General good occupational hygiene practices
- Gloves
- Certified safety clothing and shoes
- Chemical protective suit
- Eye protection
- Good general ventilation
- Regular training in workplace hygiene practice and proper use of PPE

[2] Closed pipe system, closed reaction vessels

Use in biotechnology –Use in biogas production

Use	Stage	Form of substance	Duration (min)	Frequency (no of shifts per year)	Inhalation exposure			Risk Management Measures[1]			
					No of data points/standard deviation	RWC (μg Co/m^3) (Air concentration data)	RWC 8h TWA(μg Co/m^3) (incl. weighting for RPE and exposure duration)	Contained	Automated	LEV	RPE
Formulation of mixtures for use in biogas production	Raw material handling	Solid, powder / dust ; Aqueous solution	480	24	6/1	-	0.5	no	no	90% effectiveness	no
	Formulation of solutions	Aqueous solution	480	24	-	-	5 (MEASE)	yes[2]	semi	90% effectiveness	no
	Production of solid formulations	Solid	480	24	6/1	-	0.5	yes[2]	no	90% effectiveness	no
	Filling of solutions	Aqueous solution	480	24	6/1	-	0.5	no	no	no	no

Use	Stage	Form of substance	Duration (min)	Frequency (no of shifts per year)	Inhalation exposure			Risk Management Measures[1]			
					No of data points/standard deviation	RWC (μg Co/m^3) (Air concentration data)	RWC 8h TWA(μg Co/m^3) (incl. weighting for RPE and exposure duration)	Contained	Automated	LEV	RPE
	Packaging of solid formulations	Solid, powder / dust	480	24	6/1	-	0.5	no	no	90% effectiveness	no
	Cleaning & Maintenance	Solid, powder / dust	480	24	106/4.23	82 (analogous data)	8	no	no	no	APF=10-40[3] 90%-97.5% effectiveness [3]
Industrial use in biogas production	Dosing of solid material	Solid	15	240	6/1	-	0.02	no	no	no	no
	Dosing of liquid material	Aqueous solution	15	240	6/1	-	0.02	no	no	no	no

Use	Stage	Form of substance	Duration (min)	Frequency (no of shifts per year)	Inhalation exposure			Risk Management Measures[1]			
					No of data points/standard deviation	RWC (µg Co/m^3) (Air concentration data)	RWC 8h TWA(µg Co/m^3) (incl. weighting for RPE and exposure duration)	Contained	Automated	LEV	RPE
Professional use in biogas production	Handling of sealed bags	Massive object	15	240	6/1	-	0.02	no	no	no	no

[1] Other Risk Management Measures (incl. PPE)

- General good occupational hygiene practices
- Gloves
- Certified safety clothing and shoes
- Chemical protective suit
- Eye protection
- Good general ventilation
- Regular training in workplace hygiene practice and proper use of PPE

[2] Closed pipe system, closed reaction vessels; [3] APF=40 for cobalt di(acetate), APF=10 for other cobalt salts

Use in biotechnology – Use in fermentation and biotechnological processes

Stage	Form of substance	Duration (min)	Frequency (no of shifts per year)	Inhalation exposure			Risk Management Measures[1]			
				No of data points/standard deviation	RWC (µg Co/m^3) (Air concentration data)	RWC 8h TWA(µg Co/m^3) (incl. weighting for RPE and exposure duration)	Contained	Automated	LEV	RPE
Raw material handling	Solid, powder / dust	48	31	6/1	-	0.05	no	no	78% effectiveness	APF=10[2] 90% effectiveness [2]
Operations in closed systems	Solid, powder / dust	251	78	6/1	-	0.3	yes	no	78% effectiveness	APF=10[2] 90% effectiveness [2]
Handling at laboratory scale	Solid, powder / dust	113	34	6/1	-	0.1	no	no	78% effectiveness	APF=10[2] 90% effectiveness [2]
Handling of liquid stock solution	Aqueous solution (1 - 5 %)	199	81	6/1	-	0.2	no	no	no	APF=10[2] 90% effectiveness [2]

Other Risk Management Measures (incl. PPE)

- General good occupational hygiene practices
- Gloves
- Certified safety clothing and shoes
- Chemical protective suit
- Eye protection
- Good general ventilation
- Regular training in workplace hygiene practice and proper use of PPE

[2] Cobalt dinitrate only

Use in biotechnology –Use in animal feed

Stage	Form of substance	Duration (min)	Frequency (no of shifts per year)	Inhalation exposure			Risk Management Measures[1]			
				No of data points/standard deviation	RWC (μg Co/m^3) (Air concentration data)	RWC 8h TWA(μg Co/m^3) (incl. weighting for RPE and exposure duration)	Contained	Automated	LEV	RPE
Raw material handling	Solid ; Aqueous solution	20	8	132/4.6	168	0.7	no	no	90% Effectiveness	APF = 10 90% effectiveness
Formulation	Solid ; Aqueous solution (1 - 5 %)	21	8	-	-	1 (MEASE)	yes	no	78% Effectiveness	No
Filling	Aqueous solution (1 - 5 %)	200	12	-	1	0.4 (MEASE)	no	no	no	No
Packaging	Solid, granulate < 1 %	200	12	-	-	2 (MEASE)	no	no	no	no

Stage	Form of substance	Duration (min)	Frequency (no of shifts per year)	Inhalation exposure			Risk Management Measures[1]			
				No of data points/standard deviation	RWC (µg Co/m^3) (Air concentration data)	RWC 8h TWA(µg Co/m^3) (incl. weighting for RPE and exposure duration)	Contained	Automated	LEV	RPE
Cleaning and maintenance	Solid dust/powder	45	12	106/4.2	82 (analogous data)	0.8	no	no	no	APF = 10 90% effectiveness

Other Risk Management Measures (incl. PPE)

- General good occupational hygiene practices
- Gloves
- Certified safety clothing and shoes
- Chemical protective suit
- Eye protection
- Good general ventilation
- Regular training in workplace hygiene practice and proper use of PPE

Other / bespoke uses – Humidity indicators

Stage	Form of substance	Duration (min)	Frequency (no of shifts per year)	Inhalation exposure			Risk Management Measures[1]			
				No of data points/standard deviation	RWC (µg Co/m^3) (Air concentration data)	RWC 8h TWA(µg Co/m^3) (incl. weighting for RPE and exposure duration)	Contained	Automated	LEV	RPE
Handling of liquid raw material	Aqueous solution (> 25 %)	18	160	1	0.2 (max)	0.007	no	no	no	no
Further processing	Aqueous solution (5 - 25 %)	185	160	1	0.2 (max)	0.1	no	no	no	no
Handling of humidity indicator cards or spotted bags	Massive object (1 - 5 %)	480	240	6/1.1	0.05	0.05	no	no	no	no

Other Risk Management Measures (incl. PPE)

- General good occupational hygiene practices
- Gloves
- Certified safety clothing and shoes
- Chemical protective suit
- Eye protection
- Good general ventilation
- Regular training in workplace hygiene practice and proper use of PPE

Other / bespoke uses – Water treatment chemicals

Stage	Form of substance	Duration (min)	Frequency (no of shifts per year)	Inhalation exposure			Risk Management Measures[1]			
				No of data points/standard deviation	RWC (µg Co/m³) (Air concentration data)	RWC 8h TWA(µg Co/m³) (incl. weighting for RPE and exposure duration)	Contained	Automated	LEV	RPE
Formulation	Solid, powder / dust ; Solid, crystal; Aqueous solution	480	24	132/4.62	168 (analogous data)	17	no	no	90% effectiveness	APF = 10 90% effectiveness
Use of formulation	Aqueous solution	15	240	9/1.9	4 (analogous data)	0.1	no	no	no	no
Cleaning & Maintenance	Solid, powder / dust	480	24	106/4.23	82 (analogous data)	8	no	no	no	APF = 10 90% effectiveness

Other Risk Management Measures (incl. PPE)

- General good occupational hygiene practices
- Gloves
- Certified safety clothing and shoes
- Chemical protective suit
- Eye protection
- Good general ventilation
- Regular training in workplace hygiene practice and proper use of PPE

Appendix 4: Cancer quantification

Baseline cancer cases

The estimated number of additional statistical cancer cases has been calculated using the estimates of inhalation exposure to the cobalt salts, the estimation of the number of exposed workers and the dose-response relationship.

The estimates of inhalation exposure to the cobalt salts are based on the information provided in the exposure scenarios of the registration dossiers (CoRC, 2018). Typical (median) and RWC exposure levels were used in the calculation, assuming that 90% of the companies in each sector would be operating at typical exposure levels and 10% at RWC levels. The estimates for the number of exposed workers were based on the data provided by industry (CoRC, 2017).

The calculation of excess cancer risk for workers was carried out by applying the dose response relationships established by RAC (see section B.10).

The formula for the calculation of excess risk is presented below:

$$Excess\ cancer\ risk\ (40\ years) = exposure\ level\ \times 1.05\ (mg\ Co/m^3)^{-1}$$

The outcome of this calculation is the individual excess cancer risk over a 40-year period. On this basis, the annual number of estimated cancer cases was calculated. Accordingly, the following formula was used to calculate the estimated cancer cases:

$$Estimated\ cancer\ cases\ (year) = \frac{excess\ cancer\ risk \times\ number\ of\ workers}{40\ years}$$

Table 6 in section 1.4 (Baseline) of the restriction report gives the estimated cancer cases for 1 year of exposure per sector of use.

In the calculations the following assumptions were applied:

1) *Aggregation of uses*: When exact numbers of workers per use were not available, the estimated cancer cases are calculated based on the highest exposure values within the uses covered.

2) *Manufacture and use of catalyst:* 8 of the 15 companies in these sectors are assumed to be using the cobalt salts as catalysts and 7 companies manufacturing catalysts. The exposed population is assumed to be 400 in both sectors out of total of 800.

3) *Surface treatment*: The estimated number of workers in surface treatment sector is 7400, which are allocated as follows: 74 workers for formulation (assuming that there are around 30 sites for formulation, i.e. 1% of the total number of sites). Based on the assumption that the overall EU surface treatment sector is split 80% for galvanisation and 20% for plating (CDI, 2012)[27], the number of workers for each use was calculated by applying these proportions to the remaining number of workers in the sector.

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[27] This includes both electroplating and manual brush plating.

4) *Formulation and use in biogas production*: 10% of the total number of companies is allocated to formulation and industrial use and 90% to professional use in biogas production.

5) *Use in fermentation, biotech, scientific research and standard analysis*: 30% of the companies in the biotech sector (and workers) are assumed to be operating at risk levels below 10^{-5}, and consequently not to be affected by the restriction.

6) *Formulation and use in feed grade materials*: 4 100 companies (out of total of 4 400) are assumed to operate at risk levels below 10^{-5}. The available exposure and risk levels are considered to be representative for the 300 companies involved in the formulation of cobalt-containing preparations and premixtures with a cobalt concentration above 1%.

Human health impacts

RO1 and RO2

For the estimation of the human health benefits (value of avoided cancer risk), the following steps were applied:

1) The number of estimated cancer cases was calculated based on RWC and typical exposure levels.

2) The reduction in the exposure, risk and corresponding cancer cases was calculated assuming that companies would reduce the typical or RWC exposure levels as much as indicated by the effectiveness of a set of RMMs that is required to reach the reference exposure level for RO1. For RO2, the reduction is derived directly from the effectiveness of the required set of RMMs.

3) The number of affected companies are the same as described for the economic impacts (see section 2.4).

4) The average reduction in risk would be based on the effectiveness of the risk management measures required to meet the reference exposure level.

5) The starting point for risk reduction is the RWC level for the first 10% of the companies (from the total number in that sector) and the typical exposure level to the rest of the affected companies.

6) The share of affected workers is the same as for the companies in that sector.

7) The cancer cases were divided into lung cancer (50%) and other cancers (50%) based on the respirable vs. inhalable fraction (see appendix 2).

8) The number of fatal and non-fatal cancer cases was estimated based on the average mortality rates in the EU-28. The estimated number of fatal lung cancer cases is 82.8% for lung cancer, and 50% for other cancers[28] (IARC, 2012).

9) The monetary value was calculated based on the willingness-to-pay values (WTP). As recommended by ECHA guidance, WTPs of €5 million [upper bound] for the value of a

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[28] http://globocan.iarc.fr/old/FactSheets/cancers/lung-new.asp

statistical life and €410 000 for the value of cancer morbidity were used. These were further adjusted to the 2018 price level using an appropriate EUROSTAT GDP deflator index.[29]

10) The adjusted value of a cancer case considering the respirable/inhalable fraction and mortality rate is €3 700 000.

The same assumptions on data as for the baseline were applied also for quantifying the human health impacts. The results are presented in Tables 12 and 13 in section 2.5 (Human health impacts) of the restriction report.

<u>Derogations</u>

To quantify the impacts of the derogations, the health impacts were first estimated for all the companies. After that the impacts on companies (and workers) expected to benefit (be affected) from the derogation were deducted from the results and presented separately.

GDP deflator

The GDP deflator is a measure of price inflation. It is calculated based on the application of nominal GDP and real GDP. In this report, Nominal GDP values refer to the year 2017 Q4 in European Union, which is 108.60. The Real GDP values for value of cancer cases refer to the year 2012 Q1 in European Union, which is 102.48. These values are based on EUROSTAT GDP deflator index.[30]

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[29] https://echa.europa.eu/documents/10162/13630/echa_review_wtp_en.pdf

[30] https://tradingeconomics.com/european-union/gdp-deflator

Appendix 5: Potential RMMs to be implemented

Table x below shows a list of potential RMMs to be implemented to reduce exposure to the cobalt salts. The list has been compiled from information provided by manufacturers and downstream users related to RMMs introduced in the last five years at their worksites and potential additional RMMs under consideration. No information on the effectiveness of the RMMs in reducing exposure to workers has been provided, unfortunately. The costs of RMMs are provided, including:

- an estimated range of costs of the measure (both capital expenditure and yearly operational costs) for the relevant sectors,
- an assessment of potential variation in costs between different individual sites, and the factors that may affect this variation, and
- an assessment of the additional side-benefits that may be provided by implementing these measures (i.e. an description of the proportion of the costs attributed to just the cobalt salts).

The Dossier Submitter consulted with internal engineering experts at Wood Environment & Infrastructure Solutions UK Ltd on these measures. While this was not able to provide a validation of the cost values quoted from the eftec (2018b) study, a range of factors were identified that could potentially impact the costs at individual sites and result in possible differences between different locations.

The factors influencing the overall costs of the different RMMs include the following considerations:

- Site size (production capacity) – i.e. volume of material manufactured/used
- Technical measures currently in place i.e. whether technical measures involve new build/ or retrofit
- Location (e.g. geographical/country-specific factors)
- Local supply chain and logistics (e.g. difference in delivery and installation costs)
- Environmental conditions dependent on location (e.g. sensitive receptors, etc.)
- Local Regulatory requirements (e.g. relating to health and safety)

To assess the potential differences in costs between sites, and the potential side benefits of the technical measures considered, the information provided by industry through their Call for Evidence (CfE) responses and the interviews conducted for this dossier have been reviewed.

It should be noted that limited information on the details of individual facilities (e.g. capacity, operational practices, complete breakdown of chemical substances used) was obtained due to confidentiality requirements of individual companies and trade associations. Therefore, a fully quantitative analysis was not possible.

In this appendix the dossier submitter presents information on technical measures that are being implemented, or considered across the sectors covered in this dossier, to further reduce occupational exposure to the five cobalt salts.

Table 41: Overview of additional technical measures implemented/considered in facilities manufacturing and using cobalt salts

Activity	**Sector/use**	**Technical measure**	**Estimated Costs**		**Differences in costs between sites** *(Minimal / Moderate / Significant / Unknown)*	**Side benefits from controlling other hazardous substances** *(Minimal / Moderate / Significant / Unknown)*
			One-off investment (€)	**Operational (€/year)**		
Manufacture and processing (including chemical synthesis, reduction, hot and wet metallurgical processes)	Manufacture of cobalt salts, manufacture of chemicals, manufacture of pigments and dyes, use in biotechnology	Upgraded fume hoods	€1 000 to €10 000	None	***Minimal – Moderate*** • Cost will vary depending on current technical measures in place (i.e. retrofit vs new build) • Possible differences in production plant capacity/volumes of output (e.g. on-site manufacture by catalyst producers may be smaller-scale than at larger chemical plants • Expected that different facilities follow broadly the same manufacturing processes/steps, no specific knowledge of practices at individual plants or downstream users available • No impact expected from local geographical factors/constraints • All facilities governed by EU legislation, but possible impact of local-level regulations (e.g. on health and safety).	*Manufacture of cobalt salts:* ***Moderate*** The process(es) involves other chemical substances of potential concern (some of which will be handled in the solid/powder phase), including: • sodium carbonate • caustic soda • organic solvents • acids e.g. nitric, hydrochloric, sulphuric, acetic Quantitative information on the volumes of different compounds used in the process are not available. *Manufacture of chemicals, manufacture of pigments and dyes, use in biotechnology:* ***Unknown*** • Limited information obtained/received from industry.
		Chemical flow hood (Class C)	€10 000 to €100 000	€1 000 to €10 000		
		Full dust reduction project	€1 million to €10 million	Unknown		

Activity	Sector / use	Technical measure	Estimated Costs		Differences in costs between sites *(Minimal / Moderate / Significant / Unknown)*	Side benefits from controlling other hazardous substances *(Minimal / Moderate / Significant / Unknown)*
			One-off investment (€)	**Operational (€ / year)**		
Transfer operations including loading, unloading, weighing, sampling (cobalt salts in powder form)	Manufacture, Manufacture of chemicals, manufacture of catalysts, use as catalyst, use in biotechnology, surface treatment	Down flow dispensing booth	€10 000 to €100 000	€1 000 to €10 000	***Minimal-Moderate*** • see above	*Manufacture of catalyst:* ***Moderate-Significant*** • Individual companies indicate they handle a multitude of different metals and other chemical species; • Based on industry-derived information, estimated to be 8%-38% of all operations (will be company specific and will vary year-to year). *Manufacture, Manufacture of chemicals, manufacture of pigments and dyes, use in biotechnology:* ***Unknown*** • Minimal information obtained/received from industry
		Glove bag isolator for dispensing	€100 000 to €500 000	No changes		
		Change from powder form to liquid form	€100 000 to €500 000	€10 000 to €100 000		
		Closed transfer system	€1 million to €10 million	No changes		
Mixing or blending in batch processes (cobalt salts in solid form)	Manufacture, of cobalt salts, manufacture of chemicals, manufacture of catalysts, manufacture of	Ventilation fan in batch preparation workplace	<€1 000	<€1 000	***Minimal-moderate*** • see above	*Manufacture of catalysts:* ***Moderate-significant*** • see above

Activity	Sector / use	Technical measure	Estimated Costs		Differences in costs between sites *(Minimal / Moderate / Significant / Unknown)*	Side benefits from controlling other hazardous substances *(Minimal / Moderate / Significant / Unknown)*
			One-off investment (€)	Operational (€ / year)		
	pigments and dyes, use in biotechnology, surface treatment	Dedicated solution mixing room	€10 000 to €100 000	None		*Manufacture of cobalt salt, Manufacture of chemicals, manufacture of pigments and dyes, use in biotechnology:* ***Unknown*** • Minimal information obtained/received from industry
		Installation of containment for mixing line	€10 000 to €100 000	€1 000 to €10 000		
Packaging : (cobalt salts in solid form)	Manufacture	Installation of automated packaging station (cobalt carbonate) powder	€10 000 to €100 000	€1 000 to €10 000	***Unknown*** • Minimal information obtained/received from industry	***Unknown*** • Minimal information obtained/received from industry
		Installation of a new packaging line (big bags)	€100 000 to €500 000	Unknown		
		Installation of a new packaging line (small bags)	€1 million to €10 million	Unknown		

Activity	Sector/use	Technical measure	Estimated Costs		Differences in costs between sites *(Minimal / Moderate / Significant / Unknown)*	Side benefits from controlling other hazardous substances *(Minimal / Moderate / Significant / Unknown)*
			One-off investment (€)	Operational (€/year)		
Electroplating	Surface treatment	Lids installed on plating tanks	€10 000 to €100 000	<€1 000 /year.	*Surface treatment:* ***Significant*** • Size of facilities/ operations, and concentration of cobalt salts in formulations can vary considerably between facilities; • From very small scale workshops (e.g. jewellery and watch making) to large-scale industrial facilities (e.g. servicing the automotive sector) ; • May necessitate different types/size/cost of technical measures; • No differences in costs based on geographical constraints is expected; • All facilities governed by EU legislation, but possible impact of local-level regulations (e.g. on health and safety).	*Surface treatment:* ***Moderate*** • Composition of formulation mixture (i.e. content of cobalt salts) will vary between sites and sectors; • Industry indicate the concentrations can range from 0.1%-10% (typically <0.5% in most operations); • The formulations used in surface treatment will also contain other chemical substances (e.g. chromium(III) compounds); • Specific information of composition of formulations used in different facilities/sectors was not available or provided by industry.
		Local Exhaust Ventilation (min 78% effectiveness)	€10 000-€100 000	€1 000 to €10 000/year		
		Cobalt emissions measurement system in the LEV system	€10 000 to €100 000	€1 000 to €10 000		

Activity	Sector / use	Technical measure	Estimated Costs		Differences in costs between sites *(Minimal / Moderate / Significant / Unknown)*	Side benefits from controlling other hazardous substances *(Minimal / Moderate / Significant / Unknown)*
			One-off investment (€)	Operational (€ / year)		
		Abatement scrubber units for all extraction	€100 000 to €500 000	€10 000 to €100 000		
		New tank design, incorporating larger free board and dampening extraction system	€1 million to €10 million	€1 000 to €10 000		

Appendix 6: Brief rationale for justifying risk control beyond standard BCA outcome

Economists typically rely on efficiency as welfare criterion. Harsanyi (1955) demonstrated that maximising the sum of individual expected utilities results in efficiency. Efficiency implies that the social planer values risk reductions equally no matter whether they benefit individuals exposed to high or low risks. However, there might be other welfare criteria, risk equity concerns being one of them, that the planer may want to respect.

Suppose the planer is concerned about risk equity, and particularly *ex ante* risk equity (i.e. he dislikes that some individuals bear larger risks than others). Given this concern, the planer may then adopt any of the following priorities:

1. Utilitarian planer: Reducing risk to an individual at a higher risk level is just as valuable as reducing risk to an individual at a lower risk level;
2. Prioritarian planer: Reducing risk to an individual at a higher risk level is somewhat more valuable than reducing risk to an individual at a lower risk level;
3. Maximin planer: Reducing risk to an individual at a higher risk level is infinitely more valuable than reducing risk to an individual at a lower risk level.

In what follows we adopt an Atkinson inequality aversion measure to value risk reductions to different types of individuals exposed (Bovens & Fleurbaey 2012; Adler 2016). Importantly, the approach allows exploring different priorities of the planer.

The setup is as follows.

- Consider two types of individuals h(igh risk) and l(ow risk) (extending to more types is straightforward).
- The planer seeks to maximise social welfare $w(.)$ which is a function of individual excess lifetime cancer risks. Specifically we assume that the expected disutility of bearing the risk p can be written as $E[u_i] = 1 - p_i$ for $i = l, h$.
- The utilitarian planer is simply summing up all expected utilities to determine welfare, i.e. $w = (1 - p_h) + (1 - p_l)$; all else being equal he thus prefers a situation *A*(fter) over a situation *B*(efore) iff $w^A = (1 - p_h^A) + (1 - p_l^A) > w^B = (1 - p_h^B) + (1 - p_l^B)$. This does however not preclude a situation in which the high risk type is at the same (or higher) level of risk in situation *A* (compared to *B*), i.e. $p_h^B \leq p_h^A$ is permissible.
- Now, we transform the expected utilities using an Atkinson function: $\varphi_\alpha(E[u_i]) = (1 - \alpha)^{-1}[E[u_i]^{(1-\alpha)} - 1]$ for $\alpha \geq 0, \alpha \neq 1$, and $\varphi_\alpha(E[u_i]) = \log(E[u_i])$ for the special case $\alpha = 1$, where α is an inequality aversion parameter.
- Observe that for $\alpha = 0$ the Atkinson transformation results in the same $w(.)$ than the utilitarian planer would apply. In general, the social welfare function becomes $w_\alpha = \varphi_\alpha(E[u_h]) + \varphi_\alpha(E[u_l]) = (1 - \alpha)^{-1}([(1 - p_h)^{(1-\alpha)} - 1] + [(1 - p_l)^{(1-\alpha)} - 1])$.
- To illustrate the effect of α on welfare, suppose the high and low risk types face a before risk of $\langle p_h^B = 0.2\,;\, p_l^B = 0.1\rangle$.
- Further, assume that the planer is moderately inequality averse ($\alpha = 0.5$) and faces two alternative options *A1* and *A2*, which would result in $\langle p_h^{A1} = 0.15\,;\, p_l^{A1} = 0.1\rangle$ and $\langle p_h^{A2} = 0.2\,;\, p_l^{A2} = 0.05\rangle$, respectively. If the implementation costs were the same, the utilitarian planer would find both options to be identically good:

$$\Delta w_{\alpha=0}^{A1} = (1 - \alpha)^{-1}\left[\left((1 - p_h^{A1})^{(1-\alpha)} - 1\right) - \left((1 - p_h^B)^{(1-\alpha)} - 1\right)\right] = 0.05$$

$$\Delta w_{\alpha=0}^{A2} = (1 - \alpha)^{-1}\left[\left((1 - p_l^{A2})^{(1-\alpha)} - 1\right) - \left((1 - p_l^B)^{(1-\alpha)} - 1\right)\right] = 0.05$$

- Not so the Prioritarian planer:

$$\Delta w^{A1}_{\alpha=0.5} = (1-\alpha)^{-1}\left[\left((1-p_h^{A1})^{(1-\alpha)}-1\right)-\left((1-p_h^{B})^{(1-\alpha)}-1\right)\right] = 2\left[\sqrt{0.85}-\sqrt{0.8}\right] \approx 0.055 >$$

$$\Delta w^{A2}_{\alpha=0.5} = (1-\alpha)^{-1}\left[\left((1-p_l^{A2})^{(1-\alpha)}-1\right)-\left((1-p_l^{B})^{(1-\alpha)}-1\right)\right] = 2\left[\sqrt{0.95}-\sqrt{0.9}\right] \approx 0.052.$$

From this toy example it can be seen that a modestly inequality averse planer assigns roughly $s = \frac{\Delta w^{A1}_{\alpha=0.5}/\Delta w^{A2}_{\alpha=0.5}}{\Delta w^{A1}_{\alpha=0}/\Delta w^{A2}_{\alpha=0}} \approx \frac{0.055/0.052}{0.050/0.050} = 6\%$ more social value to a situation in which the risk of the high risk type's risk is reduced by a specified amount (*A1*) vs one in which the low risk type's risk is reduced by the same amount (*A2*).

As $\frac{\partial s}{\partial \alpha} > 0$, it follows that the choice of α determines *how much more* value a specific reduction has if it accrues to a high vs low risk type. This can then be used to scale up the economic benefit of risk reduction as derived under the standard BCA approach. In sum, the approach allows expressing concern for risk equity in monetary terms *without* making any assumptions about individuals' preferences for money-risk trade-offs, i.e. without assigning different WTP values for different levels of risk.

The approach has a number of noteworthy implications. The most important ones are:

1. By accommodating risk equity as additional decision criterion, the optimal decision is no longer guaranteed to be efficient (Rheinberger & Treich, 2017). In theory this implies the decision maker prefers a situation in which *N* statistical cases are avoided among a group of highly exposed individuals over one in which *N* + *x* statistical cases are avoided among a group of less exposed individuals;
2. The approach is expressing the social planer's concern about individual risk exposure but ignores that reductions in risk come at a cost which may affect other dimensions of individual welfare (e.g. reduction in wages, job security, etc.). In that sense, the approach is safety paternalistic;
3. The approach focuses on excess risk from exposure to cobalt salts, ignoring that prevailing background risks may be much larger. One may thus ask whether the idea of risk equity is appealing, if excess cancer risk from exposure to cobalt is small compared to the total cancer or mortality risk.

Appendix 7: Biomonitoring of cobalt

Occupational exposure to cobalt can be biomonitored by measuring Cobalt in urine. Also blood Cobalt analysis has been used earlier, and e.g. the ACGIH and the MAK Commission had BEI and EKA values (respectively), for blood cobalt. These were, however, withdrawn in their latest updates (ACGIH 2014; MAK, 2012). This is because the levels of cobalt in blood are about 10 times lower than in urine, and it is therefore a less sensitive and reliable method for biomonitoring of Cobalt than urine analysis. Also, non-invasiveness of the sampling is considered important.

Background urinary Cobalt levels have been reported in literature from several countries:

- In the NHANES survey (latest 2015-2016) in 20+ years old adults, 95th percentile urinary Cobalt levels was 1.41 µg/l, females showing higher levels than males (1.82 vs 1.08 µg/l, respectively) (NHANES, 2019).
- In the Belgian population, the 95th percentile was 1.0 µg/l (n=1022, Hoet et al. 2013).
- Frery et al. (2010) report a 95th percentile of 1.13 µg/g crea (~1.3 µg/l) for the French population (n=1991).
- Similarly, 95th percentiles in UK and Italian populations were 1.04 and 2.24 µg/l, respectively (Morton et al., 2014, Aprea et al., 2018). In both cases, females showed higher levels than males. In Finland, a reference limit for occupationally non-exposed population has been set as 25 nmol/l (=1.5 µg/l) based on the 95th percentile measured in a Finnish non-occupationally exposed population (n=118) (FIOH, 2012).
- ANSES has recently identified a reference limit of 2 µg/l for women and 0.7 µg/l for men (ANSES, 2018).
- Median urinary Cobalt levels in general population have been in different studies at the level of ~0.2-0.5 µg/l. Metal prothesis may increase urinary cobalt levels in non-occupationally exposed population.

There are several research papers reporting correlations between air Cobalt levels in the workplace air and urinary cobalt levels (see table 2). Most of them have studied exposure to cobalt metal in hard metal industry. These have been used to set the ACGIH BEI level or the German EKA levels for cobalt. ACGIH (2014) calculated that a TLV level of 20 µg/m^3 corresponds urinary cobalt levels of 15 µg/l in post-shift urinary samples in the end of the work-week. The same correlations have been used by FIOH (2012) to set their biological action limit value of 130 nmol/l (=7.7 µg/l) corresponding the air level of 10 µg/m^3. The MAK Commission (Angerer, 1994; Angerer et al., 2006) calculated following EKA levels for urinary cobalt:

Table 1: German EKA levels for U-Co

Cobalt levels in workplace air (µg/m^3)	urinary Cobalt levels (µg/l)
10	6
25	15
50	30
100	60
500	300

ANSES, on the other hand, used data from Nemery et al. (1992) and Lison et al. (1994) and recommended a BLV of 5 µg/g creatinine (~5.7 µg/l), which was calculated to correspond to the French OEL of 2.5 µg/m^3.

It should be noted that most correlation equations published in literature are based on the measured data at air concentrations usually clearly above 20 µg/m^3. Therefore, estimation of urinary levels corresponding air levels of 1 µg/m^3 and below using these correlation equations includes uncertainties. Equations used by ACGIH (2014) in their BEI documentation, or used by the German MAK Commission in their EKA calculations (MAK, 1994, 2005), result in urinary Cobalt levels close to or even below the general population reference limits when applied for 1 µg/m^3 air levels. Using the correlation equation published by Lison et al (1994), the air level of 1 µg/m^3 can be calculated to correspond urinary Cobalt level of 2.75 µg/g creatinine (~3 µg/l) and the air level of 0.5 µg/m^3 can be calculated to correspond 1.78 µg/g creatinine (~2 µg/l). In all cases, the levels are very close to the population background levels. This means that individual background from other sources may complicate the interpretation of the results at these levels and simple comparison of individual samples to general population reference limits (which are usually based on 95th percentiles observed in non-occupationally exposed population) might not be enough to detect these exposures. On the other hand, urinary levels clearly exceeding general population reference limits (1-2 µg/l) are likely to indicate occupational exposure to the air levels of ≥1 µg/m^3, although dermal contamination (and hands-to-mouth exposure) may also significantly contribute to total systemic Co levels. Since there is some cumulation of cobalt over the course of the workweek, the samples are recommended to be taken post-shift in the end of the workweek

Table 2 Published correlations between air and urinary cobalt levels

Regression: Co_{urine} (µg/l)= Co_{air} (µg/m^3) + b (correlation coefficient)	Reference
Co_{urine} = 0,70xCo_{air} + 0,7 (0,81)	(Alexandersson ja Lidums 1979; Alexandersson 1988)
Co_{urine} = 0,67 Co_{air} + 0,9 (0,99)	(Ichikawa, Kusaka et al. 1985)
Co_{urine} = 0,704 Co_{air} - 0,804 (0,805) Co_{urine} = 0,679 Co_{air} - 0,936 (0,812)	(Scansetti et al., 1985)
Co_{urine} = 0,766 Co_{air} - 0,39 (0,83)	(Stebbins et al., 1992)
Co_{urine} = 0,29 Co_{air} + 0,8 (0,83) Co_{urine} = 0.7 Co_{air} + 0.8 (0,80)	(Scansetti et al. 1998) (Scansetti et al. 1998)
Co_{urine} = 15,3 Co_{air} +54,1*# (0,74)	(Linnainmaa ja Kiilunen 1997)
Co_{urine} = 0.34 Co_{air} + 19.9# (0,61)	(Angerer, Heinrich et al. 1985)
Log Co_{urine} (ug/g creat)=0,63 log Co_{air}+0,44	(Lison et al., 1994)

*U-Co expressed as nmol/l, # clearly not applicable at air Co levels below the current OELs (10-20 µg/m^3)

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Appendix 8: Comparison between nickel and cobalt salts

Background: In 2016, RAC decided to base the dose-response of cobalt salts on linear extrapolation even thought there was evidence suggesting a threshold based MoA. Because it was not possible to identify a true threshold below which no risk exists, linear approach was chosen as default recognizing its conservativity. Since then, MoA based threshold approach was adopted by RAC for the occupational limit value setting, and applied for inorganic nickel compounds and benzene, which are known human carcinogens. This approach is described in the recent appendix to REACH guidance Chapter R8 (https://echa.europa.eu/documents/10162/23047722/draft_appendix_r8_oels_rac_201903_en.pdf/6c2b6c54-7c84-acdf-38bc-6c0fcad4260d). In this document, the applicability of threshold approach, as described in the recent R8 appendix and applied in the case of setting an OEL for nickel, is considered. Comparison to inorganic nickel compounds is made and is based on RAC opinion and ECHA background document on inorganic nickel compounds.

Evidence	**Nickel compounds**	**Cobalt salts**	**Comments**
Evidence on in vitro mutagenicity	Bacterial mutagenicity tests negative. Weak positives in mammalian cell mutagenicity tests has been explained by effects in e.g. DNA methylation.	Bacterial mutagenicity tests generally negative. In mammalian cell systems, recent OECD tests negative, some earlier positives reported.	RAC concluded nickel has not shown clear direct mutagenicity. The same conclusion can be made also for cobalt.
Evidence on in vivo mutagenicity	No studies reported.	Higher number of k-ras mutations (G to T transversions at codon 12) observed in lung tumors caused by cobalt sulphate. This is, however, considered to support indirect DNA damage caused by oxidative stress (NTP, 1998).	For both: no in vivo evidence of direct mutagenicity.
Evidence on in vitro genotoxicity	Several studies have reported the induction of chromosome aberrations (CA), sister chromatid exchange (SCE), micronuclei, DNA strand breaks and aneuploidy as well as spindle-inhibiting effects. Also an effect on cell transformation, anchorage independence and loss of cell communication observed in some studies.	Consistently positive responses in Comet assay and other tests measuring DNA strand breaks, both positive and negative results from *in vitro* MN and CA tests, one study shows induction of SCEs. Overall, Co salts are able to induce DNA strand breaks and chromosomal damage in vitro.	Both show evidence on genotoxic effects *in vitro*.
Evidence on in vivo genotoxicity	Although the data are not consistent across all the studies, overall, there are *in vivo* data confirming the *in vitro* clastogenicity	Co salts are genotoxic *in vivo* after i.p. administration causing micronuclei, aneuploidy, oxidative DNA damage. Data	Both show evidence on genotoxic effects *in vivo*.

	of nickel compounds (Positive comet assay results and induction of oxidative damage, variable results from CA and MN tests).	on oral administration inconclusive. K-ras mutations in lung tumors (see above) indicate oxidative damage.	
Mechanistic data on genotoxicity	Data on following mechanisms available: 1) interference with cellular redox regulation and induction of oxidative stress: ROS generation demonstrated *in vitro*, in addition, there is *in vivo* data to support indirect mechanisms resulting in DNA damage in vivo (e.g. Kawanishi et al., 2002 and Mayer et al., 1998 studies, see RAC recommendation on nickel OEL). In addition, recent quantitative *in vivo* data showing activation of inflammatory pathways at dose levels below the levels in which genotoxic pathways are activated (Efremenko et al., 2014 and 2017). 2) inhibition of DNA repair systems: there *are in vitro* studies showing interference with DNA excision repair (e.g. Hartwig et al., 1994) 3) dysregulation of signalling pathways and alteration of the epigenetic landscape. Nickel has been shown to have a weak affinity to DNA but high affinity to proteins (particularly histones and protamines) shown *in vitro*. Complexing of Ni with heterochromating has been shown to result in e.g. gene silencing and DNA hypermethylation *in vitro*. Strongest epigenetic effects have been associated with HIF-1, and Ni results in the activation of HIF-1α related genes. Modification of histones has been also demonstrated *in vitro*.	There are several *in vitro* studies supporting following mechanisms behind the genotoxicity of cobalt salts (see RAC (2016): 1) induction of ROS and oxidative stress; there are several in vitro studies showing induction of ROS by Co (e.g. Patel et al., 2012, Kirkland et al., 2015). Also some evidence on the induction of ROS together with inflammation *in vivo* after Co exposure (Dick et al., 2003). Evidence on oxidative lesions in lung tumors caused by Co (NTP, 2014). 2) Inhibition of DNA repair: *in vitro* studies Co seems to inhibit the catalytic activity of DNA repair proteins, like XPA and PARP *in vitro*. Also DNA binding ability of p53 has been shown be modulated by Co. Like Ni, also Co has a high affinity to proteins. Effect on topoisomerase II enzyme has been also proposed. 3) Up-regulation/stabilization of hypoxia-inducible factor (HIF-1a). Several studies in vitro studies providing evidence that Co is a strong inducer of HIF-1α. HIF-1α role in Co induced lung response demonstrated also *in vivo*. Activation of HIF-1α seems to be different from ROS formation.	Both have extensive mechanistic databases supporting indirect genotoxicity. Mechanisms of the genotoxicity of nickel concluded to be multifactorial. The same seems to apply also to cobalt. In the case of nickel there are additionally dose-response data related to genotoxic mechanisms. This is missing in the case of Cobalt.

		Unpublished Toxys report (Hendriks et al., 2019) submitted during public consultation supports previous data on the induction of oxidative stress and activation of HIF-1ɑ pathways after exposure to soluble Co compounds *in vitro*. The same exposure did not, however, resulted in the activation of DNA damage reporter genes Bscl2 and Rtkn. No clear effects were seen in p53 signalling pathway or in unfolded protein response, either.	
Animal carcinogenicity data	Poorly soluble nickel compounds (nickel subsulfide and nickel oxide) have caused lung cancer at all dose levels tested starting from 0.11 or 0.5 mg Ni/m3, respectively. Soluble nickel sulfate did not show any increase in tumour frequencies in animal tests at doses of 0.6 to 2.2 mg Ni/m3. Ni metal, oxide and subsulphide, but not soluble Ni sulphate, have caused pheochromocytomas in rats. Findings not considered relevant for humans, secondary mechanisms (related to e.g. hypoxia) likely to play a role.	Cobalt sulphate caused increased lung cancer incidence in rats and mice at all doses of 0.3-3.0 mg/m3 (i.e. 0.067-0.67 mg Co/m3). Co metal caused lung cancer in mice and rats at the doses of 1.25-5 mg/m3. Cobalt sulphate caused some increase also in pheochromocytomas, albeit less clear as metallic Co. Mechanisms likely to be secondary and similar to Ni.	Both are clear animal lung carcinogens. Systemic tumours (caused by both) can be explained by secondary mechanisms.
Human carcinogenicity data	Positive evidence from humans both for upper respiratory tract (nasal) cancer and lung cancer. A statistically significant increase in the risk of lung cancer (OR = 2.5) was observed at cumulative dose of 1.6 mg/m3-year of soluble Ni.	Evidence on carcinogenicity in humans inconclusive. In Marsh et al (2017) study, the highest cumulative doses in exposed workers were ≥0.128 mg/m3-year.	
In vivo dose-response data on non-cancer effects	In carcinogenicity study in animals, lowest concentration tested (0.11 mg/m3) caused both inflammation and increased incidence of cancer (LOAEC for inflammation and	LOAEC for lung inflammation and proteinosis for cobalt salts is 0.067 mg Co/m3, which is the same as LOAEC for lung tumors.	A 13 week inhalation study showing a NOAEL for inflammation and local DNA strand breaks was used

	cancer). 13 wk inhalation exposure study with nickel subsulfide gave a NOAEC (0.04 mg/m3) for lung inflammation and for the induction DNA strand breaks in lungs.		supporting data for the setting of PoD for nickel. Similar data is not available on cobalt.
Setting of MoA based threshold/limit value (approach used for Ni and whether the same approach can be used for Co)	Soluble sulphate: NOAEC based on inflammation. Subsulfide: LOAEC based on inflammation and cancer. 13 wk inhalation study was used as supporting data, showing NOEAC for inflammation and DNA strand breaks of 0.04 mg/m3. HEC based on MPPD model and retained doses was calculated. AFs of 3 and 2 was applied to cover interindividual differences and the severity of the effect. Comparison to epidemiological data did not show higher sensitivity of humans (interspecies AF=1). Since nickel has shown to cause also nasal cancer, OEL for inhalable fraction was derived based on epidemiological data. Data on proportions of respirable vs inhalable dust in occupational settings was used to support $OEL_{inhalable}$).	Also cobalt genotoxicity seems to be caused by secondary mechanisms. Inflammation is likely to play a role in the MoA of genotoxicity and carcinogenicity. LOAEC for inflammation is 0.067 mg/m3, no NOAEC is available. If an AF of 2.5 is used for interspecies differences, 5 for worker intra-species differences, and 5 for dose-response/severity, a reference exposure value of 0.00054 mg Co/m3 (rounded as 0.0005 mg Co/m3) can be derived for the respirable fraction. Since there is no *in vivo* dose response data on the local genotoxicity of cobalt nor data allowing the derivation of N(L)OAECs for these genotoxic effects in relation to the N(L)OAECs for pulmonary inflammation, genotoxic effects at the levels below the threshold for inflammation cannot be totally excluded. Therefore, it is not possible to set a mode of action based threshold for the lung carcinogenicity of cobalt.	Lack of in vivo dose response data on the genotoxicity of cobalt prevents setting a MoA based threshold for Co.

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Appendix 9: Impacts of change from the REV to TWA

The change from the reference exposure value (REV) to 8 hour time-weighted average (8hTWA) recommended by RAC and SEAC affects the assessments of restriction options 1a, b, c and d. The main differences between these two limit values are the familiarity of the concept to the industry, and the frequency adjustment allowed to be made for the REV.

Based on the comments received in the public consultation, the concept of 8hTWA is preferred by the industry as it is already familiar to it due to occupational safety regulations. This improves the practicability and implementability of the restriction. The Dossier Submitter agrees that there are benefits from regulating different chemicals with similar concepts also under different legislations.

The removal of frequency adjustment may increase the number of companies affected by the restriction. This is the case for those sectors where companies would have been below the REV due to activities causing exposure that do not occur every day.

The change to 8hTWA may increase both costs and benefits of the restriction as more companies may be affected and more workers benefiting from lower exposure levels. The proportionality (expressed as cost-benefit ratio) may be slightly affected negatively, as the frequency adjustment targets the restriction to companies with highest exposure potential.

The industrial sectors with highest potential for activities that do not occur every day are:

- manufacture of catalysts,
- formulation of surface treatment solutions,
- use in fermentation,
- formulation of mixtures in biogas production, and
- use in feed grade materials.

Out of these sectors, the frequency adjusted realistic worse case exposures in the sectors of formulation of mixtures in biogas production and use in feed grade materials are fairly close to 1 µg/m3. The typical exposures are lower, which suggests that only limited number of additional companies would be affected by the restriction due to the change. None of the sectors are operating close to 10 µg/m3.

This is a simple comparison based on exposure and frequency data from the registration dossiers to illustrate possible impact of the change, and the actual number of additional companies affected workers depend on the site specific air concentrations and site specific frequencies.

Appendix 10: The costs and benefits of the restriction options 1a and 1b with different assumptions on the compliance

The results of the survey provided by the industry in the public consultation are not in-line with the assumptions made by the Dossier submitter (DS) in the restriction report. According to the DS analysis, the number of companies not in compliance with RO1a is 6. However, according to the survey provided by industry the number of companies not in compliance is significantly higher 4619. Similarly for RO1b, the number of companies not in compliance according to the BD is 1967, while industry reports that it is 6691. This discrepancy regarding the actual levels of compliance (i.e. on exposure levels) results in a significant difference in the estimated benefits and costs. Tables 1 and 2 were prepared by the DS to illustrate this difference.

Table 1: Estimated number of affected companies, human health benefits and costs as presented in the background document

	Number of affected companies (in non-compliance)	Avoided Cancer cases (per year)*	Monetised benefits (million €/yr)*	Total costs Lover bound (million €/yr)	Total costs Upper bound (million €/yr)
RO1a	6	0.02	0.086	0.002	0.007
RO1b	1967 (1961 additional to RO1a)	0.24	0.885	1,1	5,4

*These estimates have been corrected by the Dossier Submitter based on the risk assessment performed by RAC

Table 2: Estimated number of affected companies and costs based on the data from the industry survey

	Number of affected companies (in non-compliance)	Avoided Cancer cases (per year)*	Monetised benefits (million €/yr)**	Total costs Lower bound (million €/yr)	Total costs Upper bound (million €/yr)
RO1a	4619	15.4	66.2	11	567
RO1b	6691 (2072 additional to RO1a)	15.7***	67.1***	42	987

* These estimates are derived by multiplying the cancer estimate of the Dossier Submitter (as amended by RAC) for one company (0.003 cases per year for RO1a and 0.000122 cases per year for RO1b) by the number of companies affected as stated in the industry survey.

** These estimates are derived by multiplying the monetised benefit estimate of the Dossier Submitter for one company (€0.014 million per year for RO1a and €0.0004 million per year for RO1b) by the number of companies affected as stated in the industry survey.

*** These estimates are derived by adding to the estimates for RO1a the additional cases for RO1b.

Taking the estimated benefits (based on the RAC risk estimate) and the costs resulting from the data provided in the industry survey, the benefit-cost ratios derived from the industry survey and estimated by the Dossier Submitter are in the same order of magnitude. The ratios are presented in table 3.

Table 3: Benefit/cost ratios of different approaches for restriction options 1a and 1b

	Benefit/cost ratio (background document)	Benefit/cost ratio (industry survey)
RO1a	10:1 - 40:1	1:9 - 6:1
RO1b	4:5 – 1:6	3:2 – 1:15

The comparison demonstrate that the cost-benefit ratio is not significantly affected by adopting the compliance estimates from the industry survey. However, the impact on risk reduction capacity and total costs is significant. The current exposure levels in the companies have also a direct impact on the baseline cancer cases.

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