Annex XV report

PROPOSAL FOR IDENTIFICATION OF A SUBSTANCE AS A CMR CAT 1 OR 2, PBT, vPvB OR A SUBSTANCE OF AN EQUIVALENT LEVEL OF CONCERN

Substance Name:	**Cobalt(II) diacetate**
EC Number:	**200-755-8**
CAS Number:	**71-48-7**
Submitted by:	**RIVM, The Netherlands**
Version:	**August 2010**

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PROPOSAL FOR IDENTIFICATION OF A SUBSTANCE AS A CMR CAT 1 OR 2, PBT, VPVB OR A SUBSTANCE OF AN EQUIVALENT LEVEL OF CONCERN

Substance Name: Cobalt(II) diacetate

EC Number: **200-755-8**

CAS number: **71-48-7**

In addition, the proposal covers also the hydrated forms of Cobalt(II) diacetate[1].

- The substance is proposed to be identified as substance meeting the criteria of Article 57 (a) of Regulation (EC) 1907/2006 (REACH) owing to its classification as carcinogen category 2.
- The substance is proposed to be identified as substance meeting the criteria of Article 57 (c) of Regulation (EC) 1907/2006 (REACH) owing to its classification as toxic for reproduction category 2.

Summary of how the substance(s) meet(s) the C and R (Cat. 2) criteria.

Pursuant to the first ATP to Regulation (EC) No 1272/2008 (Commission Regulation (EC) No 790/2009) as of 1 December 2010, cobalt(II) diacetate will be listed as entry 027-006-00-6 in Annex VI, part 3, Table 3.2 (the list of harmonised and classification and labelling of hazardous substances from Annex I to Directive 67/548/EEC) of Regulation (EC) No 1272/2008 as carcinogen category 2[2]. The hydrous forms of cobalt(II) diacetate are also considered as carcinogen category 2 according to Annex VI, part 1.1.1.5, of Regulation (EC) No 1272/2008. According to part 1.1.1.5 (Entries of groups of substance) entries in part 3 for salts (under any denomination) cover both anhydrous and hydrous forms, unless specified otherwise.

Pursuant to the first ATP to Regulation (EC) No 1272/2008 (Commission Regulation (EC) No 790/2009) as of 1 December 2010, cobalt(II) diacetate will be listed as entry 027-006-00-6 in Annex VI, part 3, Table 3.2 (the list of harmonised and classification and labelling of hazardous substances from Annex I to Directive 67/548/EEC) of Regulation (EC) No 1272/2008 as toxic to reproduction category 2[3]. The hydrous forms of cobalt(II) diacetate are also considered as toxic to reproduction 2 according to Annex VI, part 1.1.1.5, of Regulation (EC) No 1272/2008. According to part 1.1.1.5 (Entries of groups of substance) entries in part 3 for salts (under any denomination) cover both anhydrous and hydrous forms, unless specified otherwise.

[1] According to the rules applied when establishing EINECS (Manual of Decisions, Criteria for reporting substances for EINECS, http://ecb.jrc.ec.europa.eu/documents/New-Chemicals/Manual_of_decisions.pdf): "The anhydrous form can be reported and will, by implication, represent all hydrated forms."

[2] This corresponds to a classification as carcinogen (1B) in Annex VI, part 3, Table 3.1 of Regulation (EC) No. 1272/2008 (list of harmonised classification and labelling of hazardous substances)

[3] This corresponds to a classification as toxic to reproduction (1B) in Annex VI, part 3, Table 3.1 of Regulation (EC) No. 1272/2008 (list of harmonised classification and labelling of hazardous substances).

Therefore, this classification of the substance in Commission Regulation (EC) No 790/2009 shows that the substance meets the criteria for classification as carcinogen and as toxic for reproduction, in accordance with Article 57 (a) and (c), respectively, of REACH.

PART I

JUSTIFICATION

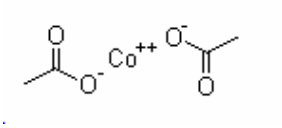
1 IDENTITY OF THE SUBSTANCE AND PHYSICAL AND CHEMICAL PROPERTIES

1.1 Name and other identifiers of the substance

Table 1: Substance identity

EC number:	200-755-8
EC name:	Cobalt di(acetate)
CAS number:	71-48-7
IUPAC name:	Cobalt(II) diacetate
Index number in Annex VI of the CLP Regulation	027-006-00-6
Molecular formula:	$C_4H_6CoO_4$
Molecular weight:	177.02

Structural formula:



This Annex XV dossier covers also the hydrated forms of cobalt(II) diacetate. According to the rules applied when establishing EINECS[4]: “The anhydrous form can be reported and will, by implication, represent all hydrated forms.”

[4] Manual of Decisions, Criteria for reporting substances for EINECS, http://ecb.jrc.ec.europa.eu/documents/New-Chemicals/Manual_of_decisions.pdf.

1.2 Composition of the substance

Information on concentration range and on any impurities is not known.

1.3 Physico-chemical properties

Table 2: Overview of physicochemical properties

Property	Value	Remarks
Physical state at 20°C and 101.3 kPa	Light-pink crystals	U.S., Department of Health and Human Services
Melting/freezing point	No data for anhydrous form, loses four H_2O at 140^{o}C for tetrahydrate form	U.S., Department of Health and Human Services
Water solubility*	Readily soluble Soluble in water	U.S., Department of Health and Human Services IPCS, 2006
Partition coefficient n-octanol/water (log value)	Not relevant	

* The water solubility of cobalt(II) diacetate in the form of a numerical value or range is not available.

2 HARMONISED CLASSIFICATION AND LABELLING

2.1 Classification according to Directive 67/548/EEC

Pursuant to the first ATP to Regulation (EC) No 1272/2008 (Commission Regulation (EC) No 790/20095) as of 1 December 2010, Cobalt(II) diacetate[5] will be included with index number 027-006-00-6[6] in Annex VI, part 3, Table 3.2 of Regulation (EC) No 1272/2008.with the following classification:

Carc.Cat. 2; R49	May cause cancer by inhalation
Repr.Cat. 2; R60	May impair fertility
R42/43:	May cause sensitization by inhalation and skin contact
Muta.Cat. 3; R68	Possible risk of irreversible effects
N; R50/53:	Very toxic to aquatic organisms, may cause long-term adverse effects in the aquatic environment

Specific concentration limits:

Classification	Concentration
Carc. Cat. 2 R49	$C \geq 0.01\%$
N; R50-53	$C \geq 2.5\%$
N; R51-53	$0.25\% \leq C < 2.5\%$
R52-53	$0.025\% \leq C < 0.25\%$

Notes:

Note 1: The concentration stated or, in the absence of such concentrations, the generic concentrations of this Regulation (Table 3.1) or the generic concentrations of Directive 1999/45/EC (Table 3.2) are the percentages by weight of the metallic element calculated with reference to the total weight of the mixture.

2.2 Classification according to Regulation EC 1272/2002

Pursuant to the first ATP to Regulation (EC) No 1272/2008 (Commission Regulation (EC) No 790/20095) as of 1 December 2010, Cobalt(II) diacetate[5] will be listed in Annex VI, part 3, Table 3.1 of Regulation (EC) No 1272/2008 (list of harmonised classification and labelling of hazardous substances) with the following classification:

Carc. 1B, H350i	May cause cancer by inhalation
Muta. 2, H341	Suspected of causing genetic defects

[5] The EC number 200-755-8 and CAS number 71-48-7 specified in Annex VI refer to the substance where cobalt has the oxidation state +2.

[6] International Chemical Identification: cobalt acetate

Repr. 1B, H360F***[7]	May damage fertility
Resp.Sens. 1 H334	May cause allergy or asthma symptoms or breathing difficulties if inhaled
Skin Sens.1 H317	May cause an allergic skin reaction
Aquatic Acute 1 H400	Very toxic to aquatic life
Aquatic Chronic 1 H410	Very toxic to aquatic life with long lasting effects

Specific concentration limits:

Classification	Concentration
Carc. 1B H350i	$C \geq 0.01\%$

M-factor: 10

Notes:

Note 1: The concentration stated or, in the absence of such concentrations, the generic concentrations of this Regulation (Table 3.1) or the generic concentrations of Directive 1999/45/EC (Table 3.2) are the percentages by weight of the metallic element calculated with reference to the total weight of the mixture.

[7] According to Annex VI (Part 1, entry 1.2.3): H360 and H361 indicate a general concern for effects on both fertility and development: 'May damage/Suspected fertility or the unborn child'. According to the criteria, the general hazard statement can be replaced by the hazard statement indicating only the property of concern, where either fertility or developmental effects are proven to be not relevant. In order not to lose information from the harmonised classifications for fertility and developmental effects under Directive 67/548/EEC, the classifications have been translated only for those effects classified under that Directive. These hazards statements are indicated by reference *** in Table 3.1

3 ENVIRONMENTAL FATE PROPERTIES

Not relevant for this type of dossier.

4 HUMAN HEALTH HAZARD ASSESSMENT

Information on the hazard properties of cobalt(II) diacetate and its hydrates is provided for information purposes only as the classification has already been concluded by TC-C&L and included in Annex VI. Please refer to Annex I of this report.

5 ENVIRONMENTAL HAZARD ASSESSMENT

Not relevant for this type of dossier.

6 CONCLUSIONS ON THE SVHC PROPERTIES

6.1 PBT, vPvB assessment

Not relevant for this type of dossier

6.2 CMR assessment

The classification of Cobalt(II) diacetate (anhydrous and hydrous forms) in Commission Regulation (EC) No 790/2009 (Carc.Cat. 2; R49: May cause cancer by inhalation; Repr.Cat. 2; R60: May impair fertility) shows that the substance meets the criteria for classification as carcinogen and as toxic for reproduction in accordance with Article 57 (a) and (c), respectively, of REACH.

PART II

INFORMATION ON USE, EXPOSURE, ALTERNATIVES AND RISKS

1 INFORMATION ON MANUFACTURE, IMPORT/EXPORT AND USES – CONCLUSIONS ON EXPOSURE

Information on production volumes and main use applications and exposure data of cobalt acetate is provided in this section. This is not meant to be an exhaustive list but it illustrates the numerous use applications of this compound and related emissions. It should be noted, that very little data concerning production volumes and exposure of cobalt acetate itself has been found. Therefore information on inorganic cobalt salts as a group is given instead. On the contrary, for the production process and use applications exclusively data for cobalt acetate are given. Some additional data were included after consultation of the cobalt industry by CDI*.

The commercial form is cobalt(II) diacetate tetrahydrate, $Co(C_2H_3\text{-}O_2)_2$ $x4H_2O$ (CAS number 6147-53-1). All information given in this chapter applies to both the hydrate and the anhydrous form (CAS number 71-48-7).

1.1 Production and use volumes

1.1.1 Production

Cobalt acetate in produced on commercial scale by dissolving cobalt(II) carbonate or hydroxide in dilute acetic acid, followed by crystallization. Also, it may be prepared by oxidation of dicobalt octacarbonyl in the presence of acetic acid (Patnaik, 2002), or from powdered Co and acetic acid (The Merc Index, 14th Edition). The commercial product is manufactured and sold in the tetrahydrate form of the compound (Patnaik, 2002).

It can be also prepared, by reflux of acetic acid solutions in the presence of cobalt(II) oxide, or by oxygenation of hot acetic acid solutions over cobalt metal (Kirk-Othmer 2010).

* The Cobalt Development Institute (CDI) is a trade association that has represented the interests of a significant proportion of the global cobalt industry for more than 50 years and has been mandated by its Board to facilitate REACH implementation by the cobalt industry. Three Cobalt REACH Consortia have been established since November 2007 to help companies involved in the manufacturing and/or importing of cobalt suibstances under REACH. There are currently 43 companies who are members of the Cobalt REACH Consortia. CoRC (Cobalt REACH Consortium LTD.), a wholly-owned subsidiary of the CDI, acts as the Secretariat to the Consortia.

Data from Cobalt Development Institute website on current production volume in Europe are presented below in Table 3. However, this data concerns probably production of cobalt metal and all forms, including inorganic salts.

Table 3: CDI Members Refined Cobalt Production (tonnes) - 2009

Member Companies	**2003**	**2004**	**2005**	**2006**	**2007**	**2008**	**2009**
Eramet, France	181	199	280	256	305	311	368
OMG, Finland	7990	7893	8170	8580	9100	8950	8850
Umicore, Belgium(1)	1704	2947	3298	2840	2825	3020	2150
Xstrata (Norway)	4556	4670	5021	4927	3939	3719	3510
Total production of cobalt, including non-EU manufacturers	27952	28922	29455	29328	29491	28901	25074

(1) Includes UMICORE Chinese production

Total refined cobalt production did not change during last 6 years, only slight fluctuations are seen. In addition, after consultation the CDI reported that manufacture and/or import facilities of the Cobalt REACH Consortia members for cobalt di(acetate) are located in Belgium, Finland, France and the UK. The total EU tonnage of cobalt di(acetate) manufactured and/or imported into Europe (i.e. relevant for REACH registration) is estimated to be in the order of several thousand tonnes per year. According to the industry the vast majority (over 94%) is used as intermediate.

As no more data for the EU market were found, data from US are given for indicative purposes. Approximately 51% of U.S. cobalt use was in superalloys, 8% was in cemented carbides, 19% was in various other metallic uses, and the remaining 22% was in a variety of chemical uses. This last group contains inorganic cobalt salts (Kirk-Othmer 2010).

Table 4: Reported U.S.A. consumption of cobalt by end use (expressed in tonnes of cobalt)

End use	2001	2002
Steel	624	543
Superalloys	4,850	3,970
Magnetic alloys	472	374
Other alloys[a]	661	W[d]
Cemented carbides[b]	720	747
Chemical and ceramic uses[c]	2,100	1,860
Miscellaneous and unspecified	63	300
Total[e]	9,490	7,790

a. Includes nonferrous alloys, welding materials, and wear-resistant alloys.

b. Includes diamond tool matrices, cemented and sintered carbides, and cast carbide dies or parts.
c. Includes catalysts, driers in paints or related usage, feed or nutritive additive, glass decolorizer, ground coat frit, pigments, and other uses. It should be noted that all cobalt dinitrate tonnage is included here among other inorganic cobalt salts.
d. W: Withheld to avoid disclosing company proprietary data; included with ''Miscellaneous and unspecified.''
e. Data are rounded off; may not add to totals shown.

United States imported 182 tonnes of cobalt salts (cobalt acetates, cobalt carbonates, cobalt chlorides, and cobalt sulphates) from Finland (Kirk-Othmer 2010).

1.1.2 Uses

In this paragraph data on uses of cobalt di(acetate) are given.

Table 5: Identified use and/or activity sectors for cobalt di(acetate) showing approximate volume estimate per use sector based on information provided by industry (CDI)*

Use and/or Activity Sector	Further information	Volume estimate per use sector (%)
Manufacture of catalysts	• Manufacture of catalysts • Hydrotreating; Oxidation catalyst; Hydrodesulphurisation; Fischer Tropsch (GTL)	>70% Main use
Production of other chemicals	• Production of other chemicals (intermediate): feed materials for other chemicals	<15% Minor use
Surface treatment **Alloys**	• Surface treatments: anodizing • Alloys: Hard metal	<10% Minor use
Production of pigments **Dyes** **Adhesion**	• Production of pigments: ceramic, anodizing • Dyes • Adhesion: rubber adhesion	<5% Minor use
Animal food supplement	• Animal health: animal food supplement, additive	<5% Minor use

Notes:
- The use and/or activity sector headings are defined by the Cobalt REACH Consortia.
- Some use categories have been combined for reasons of commercial confidentiality.
- Minor uses would correspond to the REACH tonnage bands of <100 tonnes per year.
- Use as an animal food supplement is a non-intermediate use but this use is covered by different EU legislation.
- Volume estimates are approximate and based on available information and practical working knowledge.
- Volume estimates per use or activity sector are shown as relative percentage of the total, for comparison purposes.
- Percentage estimates are indicative of the use-volume information communicated to the CoRC Secretariat in the time allowed, and relative percentages may change as further sector information is assembled.

Next to the use information provided by the Cobalt Development Institute (CDI) the following use information has been collected:

Table 6: Identified uses and/or activity sectors for cobalt di(acetate)

Use and/or Activity Sector	Further information
Manufacture of catalysts	• Manufacture of catalysts and use as catalyst[2] o By far the main use of cobalt di(acetate) is as a catalyst in the production of Purified Teraphthalate Acid which is an intermediate for the manufacture of polyester fiber. This cobalt containing liquid catalyst is generally recycled. Used in synthesis of PET monomer which is further used to produce the polymer. Possible use of cobalt di(acetate) to tint clear PET containers a light blue color. o Homogenous oxidation catalyst: Cobalt(II) carboxylates, such as the oleate, acetate, and naphthenate, are used in the liquid-phase oxidations of p-xylene to terephthalic acid, cyclohexane to adipic acid, acetaldehyde to acetic acid, and cumene to cumene hydroperoxide. These reactions each involve a free-radical mechanism that for the cyclohexane oxidation can be written as Cobalt-catalyzed oxidations form the largest group of homogeneous liquid-phase oxidations in the chemical industry.
Production of other chemicals	• Production of other chemicals (intermediate): feed materials for other chemicals
Surface treatment **Alloys**	• Surface treatments: anodizing (coloring of anodized aluminum profiles).[1;5] • Alloys (hard metals)[1]
Production of pigments **Dyes** **Adhesion** **Other**	• Production of pigments: ceramic, anodizing o Pigments for decorating porcelains (Cobalt is used in ceramic pigments and designated as underglaze stains, glaze stains, body stains, overglaze colors, and ceramic colors. The underglaze is applied to the surface of the article prior to glazing. The glaze stain uses cobalt colorants in the glaze. A body stain is mixed throughout the body of the ceramic. Overglaze colors are applied to the surface and fired at low temperatures. Ceramic colors are pigments used in a fusible glass or enamel and are one of the more common sources of the blue coloration in ceramics, china, and enamel ware.)[1;2] o Pigment: anodizing (coloring of anodized aluminum profiles).[1;5] • Pigment for oil cloth (Cotton fabric coated with a preparation of linseed oils and pigments) or other dyes. • Cobalt salts are used to improve the adhesion of rubber to steel. The steel cord must be coated with a layer of brass. During the vulcanization of the rubber, sulfur species react with the copper and zinc in the brass and the process of copper sulfide formation helps to bond the steel to the rubber. This adhesion may be further improved by the incorporation of cobalt soaps into the rubber prior to vulcanization. According to the industry cobalt di(acetate) is not used as a pure substance, but is used for synthesis of other chemicals to promote rubber adhesion.[1] • Other: o Possibly used as bleaching agent for lacquers and varnishes (used in white enamels & pale color varnishes as initial color, to enhance whiteness) o Dryer in paint and varnish. Driers are substances put into paint to make dry quickly. They are metallic salts of low-molecular-weight carboxylic acids. Hydrocarbon parts take oxygen in air and metals act as catalyst to speed up the oxidative coating. Because it is an oxidation catalyst, it is used as top driers or surface drier.[3] o Sympathetic (invisible) inks: The information printed by common laser printers equipped with invisible ink is invisible in normal condition. It can not be copied and just can been under the UV light or our special readers. Widely used for security and anti-counterfeiting of bank paper, government documents, certificates & cards and labels. Under the UV

Use and/or Activity Sector	Further information
	light (200-400nm) irradiating, the invisible ink can shine visible light (400-800nm). Short-wave UV radiation stimulates visible fluorescence printing inks, excitation wavelength 254 nm.[3]
Animal food supplement	• Additive mineral supplement in animal feed[2;4]: Cobalt salts, soluble in water or stomach acid, are added to soils and animal feeds to correct cobalt deficiencies. Cobalt salts are also added to salt blocks or pellets.

Notes:
Overview of use applications is based on Patnaik (2002), The Merc Index, 14th Edition, HSDB (2010) and Kirk-Othmer (2010), supplemented by information from comments of CDI and Cobalt Consortia member companies.

[1] Use is indicated by industry to be (mainly) as an intermediate
[2] This use is likely to be attributed to other cobalt substances than cobalt di(acetate) based on comments provided by industry
[3] This use is considered not applicable (any more) based on comments provided by industry
[4] This use is subject to another Directive
[5] This use is indicated by industry to be very minor

1.2 Exposure

1.2.1 Occupational exposure

1.2.1.1 Occupational exposure

No information specific for cobalt di(acetate) was found, but some data was provided by industry (CDI) as presented in Table 7. In this section on workers, exposure to general group of the inorganic cobalt salts is presented.

Table 7: Estimated number of downstream users of cobalt di(acetate) in EU and number of workers at these locations

Specific use and/or activity Sector	Estimated number of downstream users in EU	Estimated number of workers at these facilities in EU
Manufacture of catalysts	15 to 20	NA
Production of other chemicals	5 to 10	NA
Surface treatment **Alloys**	10 to 15	NA
Production of pigments **Dyes** **Adhesion**	10 to 15	NA
Animal food supplement	<10	NA

Notes:
- NA = not available
- The use and/or activity sector headings are defined by the Cobalt REACH Consortia.
- Some use categories have been combined for reasons of commercial confidentiality.
- There may be some overlaps/gaps in the estimate of the number of Downstream Users due to the use of traders/distributors.
- It is possible that there may be duplication so it is likely that these numbers could be artificially inflated.
- Some estimates are also based on practical working knowledge.
- The number of workers is a rough estimate as not all numbers were available.
- The numbers provided could be the total number of workers per facility.

- Some facilities may be involved in more than one use of the cobalt substance.
- Estimates may change as further sector information is assembled.

The main route of occupational exposure is *via* the respiratory tract by inhalation of dusts, fumes and mists containing cobalt. Exposures have been measured in hard-metal production, processing and use and in porcelain painting. Occupational exposure to cobalt-containing dusts can cause fibrotic changes in the lung and can precipitate asthma (IARC 1991).

1.2.1.2 Workplace concentrations and exposure measurements

A cross sectional study was undertaken in workers exposed to cobalt metal, oxides, and salts in a refinery and to a mixture of cobalt and tungsten carbide in a hard metal producing plant. Although biological monitoring of workers exposed to cobalt oxides showed higher blood and urine concentrations than in non-exposed subjects, these indices poorly reflected the recent exposure level. By contrast, when exposure occurred to soluble cobalt compounds (metal, salts, and hard metals), the measurement of urine or blood cobalt at the end of the workweek could be recommended for the assessment of recent exposure.

At the workplaces with exposure to cobalt salts inspected during this study average measured cobalt concentrations were 68 – 89 μg/m^3 (range 1 – 7700 μg/m^3) (Lison 1994).

Table 8: Characteristic, exposure conditions, and biological indices in four types of cobalt workers (Lison 1994)

	Metal (n = 35)	Salts (n = 72)	Oxides (n = 15)	Hard metals (n = 10)
Age*	32 (21-54)[ab]	28 (19-55)[a]	31 (21-55)[a]	45 (27-52)[b]
Exposure (y)*	5.9 (0.48-32.4)a	4.6 (0.31-33.3)a	7.1 (2.9-22.1)a	23.0 (10-32)b
Pack-years#	8.0 (1.3-72.1)[a]	6.2 (0.6-77.9)[a]	11.7 (2.6-65.8)[a]	8.0 (0-60.0)[a]
Monday Co-air (ug/m^3)#	433 (13-6819)[a]	68 (2-7700)[b]	210 (5-3652)[ab]	9 (2-127)[c]
Monday Co-U (ug/g creatinine)#	174.7 (15.7-2244.0)[a]	32.2 (0.8-1000)[bc]	61.6 (21.3-491.2)[ac]	13.1 (3.1-87.5)[bc]
Monday Co-B (ug/dl)#	2.3 (0.2-16.0)[a]	0.8 (0.2-12.0)[b]	1.8 (0.4-7.7)[a]	ND
Friday Co-air (ug/m^3)#	383 (17-10767)[a]	89 (1-4690)[b]	467 (23-7772)[a]	19 (1-203)[b]
Friday Co-U (ug/g creatinine)#	161.6 (13.1-1534.0)[a]	45.6 (1.6-666.1)[b]	70.0 (13.5-2037.5)[ab]	17.6 (3.0-85.6)[b]
Friday Co-B (ug/dl)#	2.8 (0.2-19.0)[a]	0.9 (0.2-10.0)[b]	1.9 (0.7-7.6)[a]	ND

Groups with the same letter(s) are not statistically different (p > 0 05).
* Median (range);
# geometric mean (range).
Co-U = postshift cobalt in urine;
Co-B = postshift cobalt in blood;
Co-Air = time weighted average airborne cobalt concentration;
ND = not determined.

Workers in a factory in the Russian Federation producing cobalt acetate, chloride, nitrate and sulfates were reported to be exposed to cobalt in dust at concentrations of 0.05–50 mg/m^3 (IARC 2006).

1.2.1.3 Regulations and guidelines for occupational exposure

Regulations and guidelines for occupational exposure to cobalt in some European countries and USA are presented in Table 9. Most countries specify that the exposure limit applies to cobalt 'as Co'; OELs for specific salts are not derived. This is probably because the toxicity is determined by cobalt cation, and not by anion (IARC 2006).

Table 9: Occupational Exposure Limit values and guidelines for cobalt

Country or region	Concentration (mg/m3)[a]	Interpretation[b]
Belgium	0.02	TWA
Finland	0.05	TWA
Germany	0.5c	TWA (TRK)
Ireland	0.1	TWA
Netherlands	0.02	TWA
Norway	0.02	TWA
Poland	0.05 0.2	TWA STEL
Spain	0.02	TWA
Sweden	0.05	TWA
Switzerland	0.1	TWA
United Kingdom	0.1	TWA(MEL)
USA[d] ACGIH NIOSH OSHA	0.02 0.05 0.1	TWA (TLV) TWA (REL) TWA (PEL)

a Most countries specify that the exposure limit applies to cobalt 'as Co'.

b TWA, 8-h time-weighted average; STEL, 10–15-min short-term exposure limit; TRK, technical correct concentration; MEL, maximum exposure level; TLV, threshold limit value;REL, recommended exposure level; PEL, permissible exposure level

c Cobalt metal used in the production of cobalt powder and catalysts, hard metal (tungsten carbide) and magnet production (processing of powder, machine pressing and mechanical processing of unsintered articles); all other uses have a TRK of 0.1 mg/m^3.

d ACGIH, American Conference of Governmental Industrial Hygienists; NIOSH, National Institute for Occupational Safety and Health; OSHA, Occupational Health and Safety Administration

1.2.2 Consumer exposure

Cobalt acetate is used for painting porcelain and glass, as a dietary supplement in animal feed and previously as an additive to beer to increase the foam head.

Since cobalt and other heavy metals have been used on hand-painted china, a study was conducted to see whether these metals are released into food under acidic conditions. Forty-six samples of porcelain dinnerware from Europe or Asia that were manufactured before the mid-1970s and had hand-painted designs over the glaze were filled with 4% acetic acid to within 7 mm of the rim and analyzed after 24 hours. Of these, 36 samples released <0.02 μg/mL of cobalt and 10 released 0.020– 2.9 μg/mL (Sheets 1998 and ASTDR 2004). The Food and Drug Administration (FDA) has not established dinnerware extraction limits for cobalt.

Cobalt, which has been added to beer to increase the foam head, has been associated with cardiomyopathies (heart disease) in heavy beer drinkers. However, according to a recent Spanish study, the low levels of cobalt presently found in beer do not make a significant contribution to the total cobalt intake in heavy beer drinkers (ATSDR 2004).

1.2.3 Man exposed via the environment

The U.S. Department of Agriculture (USDA) conducted a special exploratory study in 1985–1986 to determine the concentration of trace metals in tissue of health livestock and poultry randomly selected from those slaughtered. Between 0.6 and 5.9% of samples in the 11 production classes had levels of cobalt that exceeded the lowest reliable quantification level of 0.15 ppm (0.15 mg/kg) and the mean of positive samples ranged from 0.20 to 0.23 ppm in all classes but heifer/steer, which had a level of 1.92 ppm.

Exposure of the general population to cobalt occurs through inhalation of ambient air and ingestion of food and drinking water. In general, intake from food is much greater than from drinking water, which in turn, is much greater than from air. From the limited monitoring data available, the average concentration of cobalt in ambient air in the United States is approximately 0.4 ng/m^3. However, levels may be orders of magnitude higher in source areas. Therefore, intake to cobalt in air will vary substantially from non-source areas to areas with cobalt-related industries. Similarly, the median cobalt concentration in U.S. drinking water is <2.0 μg/L; however, values as high as 107 μg/L have been reported in surveys of water supplies. Therefore, exposure from drinking water may vary considerably from one location to another. In Canada, the daily cobalt intake of the average adult from drinking water is ≤2.6 μg; this could increase to 10 μg for those living in areas with the highest cobalt levels.

General population exposure to cobalt from food is highly variable and normally higher than intake from drinking water. Most of the cobalt ingested is inorganic; vitamin B12, which occurs almost entirely in food of animal origin, constitutes only a very small fraction of cobalt intake. The cobalt intake in food has been estimated to be 5.0–40.0 μg/day. The daily cobalt intake, including food, water, and beverages of two men that were followed for 50 weeks was much higher, 310 and 470 μg. The estimated average daily cobalt intake from diet in Canada was 11 μg/day; the intake varied from 4 to 15 μg/day between the various age/sex groups. The contributions of various food groups to cobalt intake in this study were (category, contribution of dietary intake): bakery goods and cereals, 29.8%; vegetables, 21.9%; beverages, 9.8%; milk and milk products, 9.4%; meat and poultry, 9.1%; soups, 6.4%; fruit and fruit juices, 5.0%; sugar and candies, 2.8%; fish, 2.7%; fats and oils, 2.2%; and miscellaneous, 1.1%. The average daily intake of cobalt in France was estimated to be 29 μg/day. In this study, foods were divided into nine categories. The foods accounting for the greatest contributions of cobalt intake were milk and dairy products, fish-crustaceans, and condiments-sugar oil, respectively contributing 32, 20, and 16% to the daily intake (ATSDR 2004).

2 CURRENT KNOWLEDGE ON ALTERNATIVES

No information on possible alternatives for cobalt di(acetate) was found.

3 RISK-RELATED INFORMATION

3.1 Minimal Risk Levels

The ATSDR Minimal Risk Levels (MRLs) are developed by the Agency for Toxic Substances and Disease Registry (ATSDR) together with the U.S. Environmental Protection Agency (EPA). MRLs

are intended to serve as a screening tool to help public health professionals decide where to look more closely. MRLs are based on non-cancer health effects only (ATSDR 2010).

3.1.1 Inhalation MRLs

• An MRL of 0.0001 mg cobalt/m^3 has been derived for chronic-duration inhalation exposure (>365 days) to cobalt.

An MRL for inhalation exposure to cobalt was derived for chronic duration only. The chronic inhalation MRL of 0.0001 mg cobalt/m^3 was based on a no-observed-adverse-effect-level (NOAEL) of 0.0053 mg cobalt/m^3 and a LOAEL of 0.0151 mg cobalt/m^3 (both NOAEL and LOAEL values were adjusted for continuous exposure prior to MRL derivation) for decreases in forced vital capacity (FVC), forced expiratory volume in one second (FEV_1), forced expiratory flow between 25 and 75% of the FVC (MMEF), and mean peak expiratory flow rate (PEF) in diamond polishers.

The study in diamond polishers, being a well-conducted study in humans, was selected as the critical study for the derivation of a MRL because it examined a human population and identified a NOAEL, neither of which occurred in the NTP study. The chronic inhalation MRL was derived by adjusting the NOAEL of 0.0053 mg Co/m^3 for intermittent exposure (adjusted to 0.0013 mg/m^3 to simulate continuous exposure), and applying an uncertainty factor of 10 (for human variability). It should be noted that this MRL may not be protective for individuals already sensitive to cobalt.

3.1.2 Oral MRLs

• An MRL of 0.01 mg Co/kg-day has been derived for intermediate-duration oral exposure (<365 days) to cobalt.

An intermediate-duration MRL of 0.01 mg Co/kg/day was derived based on a LOAEL of 1 mg cobalt/kg day for polycythemia as reported in a study by Davis and Fields (1958). The authors exposed six men to 120 or 150 mg/day of cobalt chloride (~1 mg Co/kg/day) for up to 22 days. Exposure to cobalt resulted in the development of polycythemia in all six patients, with increases in red blood cell numbers ranging from 0.5 to 1.19 million (~16–20% increase above pre-treatment levels). Polycythemic erythrocyte counts returned to normal 9–15 days after cessation of cobalt administration. An 8–week study in rats (Stanley et al. 1947) also reported increases in erythrocyte number, with a no-observed-effect-level (NOEL) of 0.6 mg/kg-day and a lowest-observed-effect-level (LOEL) of 1 mg/kg/day. The intermediate oral MRL was derived by dividing the LOAEL of 1 mg Co/kg-day by an uncertainty factor of 100 (10 for use of a LOAEL and 10 for human variability).

Oral MRL values were not derived for acute or chronic exposure to cobalt. An acute MRL was not derived because the reported effects in animals were serious and occurred at levels above those reported in the few human oral studies. No chronic oral studies were available in animals; the chronic studies of beer-cobalt cardiomyopathy were not used because the effects were serious (death) and because the effects of concurrent alcoholism were not controlled for. Therefore, a chronic oral MRL was not derived for cobalt (ATSDR 2004).

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ANNEXES

1 ANNEX I: HUMAN HEALT HAZARD ASSESSMENT

Information on the hazard properties of cobalt di(acetate) is provided for information purposes only as the classification has already been concluded by TC-C&L and included in Annex VI. However, the C&L proposal and the data used for this are no longer available at the ECB website. The provided information is limited to the endpoints relevant for the inclusion of the SVHC list and is based on available summaries.

The summaries used in this report are mainly copied from the ASTDR toxicological profile for cobalt (published in 2004); the IARC monographs on the evaluation of carcinogenic risk to humans for cobalt and cobalt compounds (Volume 52, published in 1991) and cobalt in hard metals and cobalt sulphate (Volume 86, published in 2006); and the Report on Carcinogens (RoC) background document for cobalt sulphate (published in 2002). The references are available in the ASTDR, IARC and RoC.

Cobalt di(acetate) is an organic salt of divalent cobalt. The behaviour of the anhydrous and hydrated forms in solution is the same, as dissolution of either results in a system containing hydrated ions and water. Although there is limited carcinogenicity, mutagenicity and reproductive studies available for both anhydrous and hydrate forms of cobalt di(acetate), numerous studies have investigated the toxicological effects of cobalt and cobalt compounds as a class. These include a number insoluble and soluble cobalt compounds. The data from soluble cobalt II salts compounds can be used to read across to cobalt di(acetate) as relevant information concerning its CMR effects because these properties are mediated by the ionic form of cobalt(II). Review of the toxicity data for a series of cobalt(II) compounds shows that toxicity is expressed in terms of Co(II) ion. Consequently, the toxicity of soluble Co(II) salt compounds is basically comparable.

1.1 Toxicokinetics (absorption, metabolism, distribution and elimination)

1.1.1 Human information

No studies were available specifically for cobalt(II) diacetate.

The following summary on the toxicokinetics of cobalt and cobalt compounds was taken from the RoC Background Document for Cobalt sulphate, published in 2002.

Cobalt is absorbed from the gastrointestinal tract, lungs, and skin. Normal levels in blood and urine in the general population are 0.2 to 2 μg/L, but concentrations greater than 200 μg/L have been reported in the urine of workers occupationally exposed to cobalt (IARC 1991, NTP 1998). Gastrointestinal tract absorption is highly variable depending on the compound, concentration, and other factors, but is estimated to range from 5% to 45% (Lauwerys and Lison 1994) and may be higher in females than in males (Christensen and Poulsen 1994). There is evidence that iron and cobalt share the same transport mechanism in the duodenum (Léonard and Lauwerys 1990). The degree of respiratory absorption in humans is unknown but varies with concentration. Some studies have shown a good correlation between concentrations in air and concentrations in urine of workers (Christensen and Poulsen 1994). Respiratory absorption of cobalt inhaled as cobalt oxide was about 30% (Lauwerys and Lison 1994). Scansetti et al. (1994) demonstrated substantial absorption of cobalt through the skin.

Once absorbed, cobalt is preferentially distributed to the liver, kidney, and heart (Léonard and Lauwerys 1990, Christensen and Poulsen 1994). Without occupational exposure, the cobalt content in the adult human body is about 1 to 2 mg. The cobalt content of bone and muscle account for 14% and 13%, respectively, of the total body burden, with the rest occurring in soft tissues (Léonard and Lauwerys 1990, IARC 1991). The highest cobalt concentrations are in the liver, because vitamin B12 is stored there; IARC (1991) reported that the cobalt concentration in the liver at autopsy ranged from 6 to 151 μg/kg, with a median value of 30 μg/kg. Patients dying of cardiomyopathy from excessive intake of cobalt-fortified beer had 10 times the normal amount of cobalt in the heart (IARC 1991).

Concentrations of arsenic and cobalt were evaluated in tissue and plasma of patients with laryngeal carcinoma (Collecchi et al. 1986). Plasma and histologically nonmalignant and malignant laryngeal tissues were obtained from each of 15 male patients with no known exposure to toxic amounts of cobalt. The cobalt concentrations in malignant laryngeal tissue (68.7 ± 7.3 ng/g dry weight, mean ± SD) were significantly higher ($P < 0.01$, paired t-test and Wilcoxon's test) than those in nonmalignant laryngeal tissue (39.6 ± 7.0). The plasma cobalt concentrations were 25-fold higher in the 15 patients with laryngeal carcinoma than in 11 apparently normal male individuals (18.27 ± 2.10 and 0.73 ± 0.10 ng/mL, respectively; $P < 0.001$, Student's t-test and Mann-Whitney U-test).Similar significant differences were reported for plasma and tissue arsenic levels. The authors reported that further studies were in progress to ascertain the clinical significance of the changes in tissue and plasma cobalt and arsenic concentrations; however, no additional publications on this subject were identified in a search of the literature since 1986.

Cobalt is excreted in the urine and, to a lesser degree, in the feces. In experimental animals, 70% or more is eliminated in the urine (IARC 1991). In humans, 28% to 56% of radiolabelled cobalt chloride was eliminated in the urine and 2% to 12% in the feces within eight days after parental administration. Between 9% and 16% of the administered dose was eliminated very slowly, with a biological half-life of about two years (Smith et al. 1972). Thus, cobalt excretion has two distinct phases: a rapid initial phase, with a half- life of a few days, followed by a slow second phase, with a half-life of a year or more (Léonard and Lauwerys 1990, Lauwerys and Lison 1994). Cobalt concentrations in the urine of workers in the Italian hard-metal industry were 10 to 100 μg/L at the beginning of the work shift, increasing to 16 to 210 μg/L at the end of the shift (Sabbioni et al.1994). Clearance from the lungs has not been studied but is expected to be rapid for soluble cobalt salts (NTP 1998).

1.2 Acute toxicity

Not relevant for this type of dossier.

1.3 Irritation

Not relevant for this type of dossier.

1.4 Corrosivity

Not relevant for this type of dossier.

1.5 Sensitisation

Not relevant for this type of dossier.

1.6 Repeated dose toxicity

Not relevant for this type of dossier.

1.7 Mutagenicity

1.7.1 Non-human information

1.7.1.1 In vitro data

The results for in vitro tests specifically for cobalt(II) diacetate and its hydrates are given in Table 10.

Table 10: Results *in vitro* mutagenicity assays.

Test system	Result[a]		Dose	Reference
	Without exogenous metabolic system	With exogenous metabolic system		
Cobalt(II) diacetate				
Inhibition of repair of UV-induced pyrimidine dimers, nucleoid sedimentation, human HeLa S-3 cells	+		100 µM	Synder *et al*. (1989)
Enhancement of cell transformation by simian adenovirus SA7, Syrian hamster embryo cells	+		0.2 mM	Casto *et al*. (1979)
Cobalt(II) diacetate tetrahydrate				
Chromosomal aberrations, human lymphocytes	-		0.6 µg/mL [2.4 µM]	Voroshilin et al. (1978)

This table is taken and modified from IARC, 2006.
+ Positive response; - negative response

Cobalt di(acetate) was found to inhibit DNA repair *in vitro* and enhanced viral transformation in Syrian hamster embryo cells. In contrast, cobalt di(acetate) tetrahydrate was found to be negative for chromosomal aberrations in human lymphocytes.

1.7.1.2 In vivo data

Cobalt di(acetate) was shown to induce DNA base damage in female and male Fischer 344/NCr rats (Kasprzak et al. 1994).

1.7.2 Human data

No studies are available specifically to cobalt di(acetate) and its hydrates.

1.7.3 Other relevant information

1.7.3.1 In vitro and in vivo data

Several other cobalt(II) salts have been investigated in different short term tests for mutagenic effects. The most studied is the water soluble cobalt(II) chloride. Few results are available for other cobalt salts.

Mutagenicity effects for cobalt(II) chloride
The following summary was taken from the IARC monograph for Cobalt in hard-metals and cobalt sulphate, published in 2006.

a) In Vitro

Cobalt(II) chloride was found to be inactive in the λ prophage induction assay, and gave conflicting results in the *Bacillus subtilis rec*+/– growth inhibition assay; when a cold preincubation procedure was used, positive results were observed (Kanematsu *et al.*,1980). Lysogenic induction and phage reactivation was found in *Escherichia coli* in the absence of magnesium. Also in *E. coli*, reduction of fidelity of DNA replication by substitution of magnesium and inhibition of protein synthesis were observed. Cobalt(II) chloride was inactive in all but two bacterial mutagenicity tests. One study gave positive results in the absence, but not in the presence, of an exogenous metabolic system, and in the second study, a preincubation procedure was used.

In bacteria, cobalt(II) chloride has been reported to reduce the incidence of spontaneous mutations and to inhibit mutations induced by *N*-methyl-*N*′-nitrosoguanidine and 3-amino-1,4-dimethyl-5*H*-pyrido[4,3-*b*]indole. It was found to be comutagenic with several heteroaromatic compounds such as benzo(a)pyrene and naphthylamine. In *Saccharomyces cerevisiae*, cobalt(II) chloride induced gene conversion and petite ρ–mutation in mitochondrial DNA but not other types of mutation.

In mammalian cells cultured *in vitro*, positive results were obtained for induction of DNA–protein cross-linkage, DNA strand breakage and sister chromatid exchange in most studies. Cobalt(II) chloride 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(II) chloride did induce gene mutations. In a single study, at the *Tk* locus in mouse lymphoma L5178Y cells, the results were negative. In most studies, in cultured human cells *in vitro*, positive results were obtained for inhibition of protein-DNA binding activities, inhibition of p53 binding to DNA and for induction of gene expression, induction of DNA strand breakage and sister chromatid exchange. Chromosomal aberrations were not observed in cultured human cells (IARC,1991). Cobalt(II) chloride induced aneuploidy in cultured human lymphocytes.

b) In Vivo

In vivo, cobalt(II) chloride administered by intraperitoneal injection induced aneuploidy (pseudodiploidy and hyperploidy) in bone marrow and testes of Syrian hamsters, micronuclei in bone marrow in male BALB/c mice, and enhanced the micronuclei frequencies induced by the three other mutagens tested. A gene expression mechanism is involved in several tissue and cellular responses induced by soluble cobalt (generally cobalt chloride) mimicking the pathophysiological

response to hypoxia, a response which involves various genes including those coding for erythropoiesis and for growth factors for angiogenesis (Gleadle *et al*., 1995; Steinbrech *et al*., 2000; Beyersmann, 2002). Up-regulation of erythropoietin gene expression was observed *in vivo* after a single intraperitoneal injection of cobalt chloride (60 mg/kg bw) into rats (Göpfert *et al*., 1995) and might be of relevance in explaining the polyglobulia noted in humans treated with high doses of cobalt (Curtis *et al.*, 1976). In Chinese hamster ovary cells, cobalt also up-regulated the expression of haeme oxygenase-1, a potent antioxidant and anti-inflammatory mediator which helps to maintain cellular homeostasis in response to stress and injury (Gong *et al*., 2001). In studies designed to explore the molecular mechanisms of gene response to hypoxia, cobalt (12 and 60 mg/kg bw as cobalt chloride) was found to up-regulate the expression of the *PDGF-B* gene in lungs and kidneys of male Sprague-Dawley rats (Bucher *et al*.,1996). Since PDGF is an important growth factor which modulates cell proliferation and the expression of several proto-oncogenes mainly in mesenchymal cells, this effect of cobalt might explain how it may exert fibrogenic and/or carcinogenic properties, but this remains to be documented.

Mutagenicity effects for other cobalt compounds

The following summary was taken from the IARC monograph for Cobalt in hard-metals and cobalt sulphate, published in 2006.

Molecular analysis of lung neoplasms of B6C3F1 mice exposed to cobalt sulphate heptahydrate showed the presence of K-*ras* mutations with a much higher frequency (55%) of G > T transversion at codon 12 than in controls (0%). This provides suggestive evidence that cobalt sulphate heptahydrate may indirectly damage DNA by oxidative stress (NTP, 1998).

Cobalt sulphate has been shown to induce chromosomal aberrations and aneuploidy in plant cells (Komczynski et al., 1963; Herich, R. 1965; Gori et al. 1957), chemical changes in bases in purified calf thymus DNA and in isolated human chromatin in the presence of hydrogen peroxide, and cytoskeletal perturbation of microtubules and microfilaments and p53 protein in mouse fibroblasts treated *in vitro*. Cell transformation of Syrian hamster embryo cells has been induced by cobalt sulphate *in vitro*.

A number of mammalian genes (metallothionein MT-IIA, heat-shock proteins hsp70, c-fos) are transcriptionally regulated by a *cis*-acting DNA element located in their upstream regions. This DNA element responds to various heavy metals, including cobalt, to stimulate the expression of these genes (Murata et al., 1999). *MT-IIA* and *hps70* but not *c-fos* RNA transcripts were increased in HeLa S_3 cells exposed to high concentrations of cobalt sulphate (> 10 μM). Metal response element (MRE)-DNA binding activity was not inhibited by cobalt sulphate in Hela cells *in vitro* while the results for heat shock element (HSE)-DNA binding activity were inconclusive. It is unknown whether MT-IIA and hps70 induction plays a role in the pathophysiological processes involved in cobalt carcinogenesis.

Cobalt sulphide particles were found to induce DNA strand breaks and alkali-labile sites in Chinese hamster ovary cells. Data on the induction of gene mutations in Chinese hamster cells by cobalt sulphide particles are conflicting. Cobalt sulphide was shown to induce morphological transformation in Syrian hamster embryo cells; the crystalline form of cobalt sulphide being more active than the amorphous form.

Cobalt(III) nitrate induced gene mutations in *Pisum abyssinicum* chlorophyll. Eight of 15 cobalt(III) complexes with aromatic ligants were found to be positive in a DNA repair assay and four among the eight were also mutagenic to *Salmonella typhimurium*. Cobalt(III) complexes with desferal-

induced scission of double-stranded DNA, and a cobalt(III) Schiff-base complex induced inhibition of zinc-finger transcription factors.

1.7.3.2 Human data

Five studies have been conducted to date on the possible cytogenetic effects induced by cobalt compounds in lymphocytes (or leukocytes) of individuals exposed to metals.

The following summary was taken from the IARC monograph for Cobalt in hard-metals and cobalt sulphate, published in 2006.

a) Sister chromatid exchange

Results of sister chromatid exchange have been obtained in two studies in which exposure was to a mixture of metals. Occupational exposure to metals was studied by Gennart et al. (1993) who determined sister chromatid exchange in 26 male workers exposed to cobalt, chromium, nickel and iron dust in a factory producing metal powder and in 25 controls, who were clerical workers, matched for age, smoking habits and alcohol consumption. Slight exposure to nickel or chromium oxides could not be excluded, since, at one stage of the production process, the metals are melted in an oven. The differences in the concentrations of cobalt in the urine in exposed persons (cobalt geometric mean, 23.6 μg/g creatinine; range, 6.4–173.1) and controls (cobalt geometric mean,.1 μg/g creatinine; range, 0.2–3.2) were statistically significant. Analysis of variance revealed that both exposure status (exposed versus controls) and smoking habits (smokers and former smokers versus never smokers) had statistically-significant effects on the sister chromatid exchange or high-frequency cell (HFC) rank values. These effects may not be attributable to cobalt alone.

Stea et al. (2000) compared sister chromatid exchange in patients who had chrome–cobalt alloy prostheses and in those with other metal alloys. The study population consisted of 30 patients with joint prostheses and 17 control subjects matched for age, sex, and exposure to occupational and environmental risk factors such as chemicals, antineoplastic drugs and traffic smog. The mean sister chromatid exchange rate in subjects with prostheses (5.2 ± 1.5) was not statistically different from that in subjects without prostheses (4.4 ± 1.3). Subjects with titanium–aluminium–vanadium alloy prostheses had a significantly higher sister chromatid exchange frequency (6.3 ± 2.3) than the controls (4.4 ± 1.3) whereas subjects with prostheses made of chrome–cobalt alloys or mixed prostheses had a higher, but not significantly, sister chromatid exchange frequency (4.7 ± 1.1 and 5.0 ± 2.1, respectively) than the controls. The number of sister chromatid exchanges was not affected by the presence of bone-cement used in prosthesis fixation nor by duration of the implant. There was no difference in the incidence of sister chromatid exchange between the two populations (those with prostheses and controls) considered globally and the considered risk factors, including smoking. The HFC values (> 9 exchanges per cell) were also recorded. Among the cases studied, three patients with implants (one with a prosthesis made of chrome–cobalt alloy and two with mixed prostheses) showed markedly elevated percentages of HFCs (> 10%). It was concluded that the indication of possible cytogenetic damage in the patient populations should be considered with caution, since the sample population was small.

b) Micronuclei and DNA damage

Burgaz et al. (2002) applied the micronucleus test to assess the effect of occupational exposure to metal alloys in both exfoliated nasal cells, and *in vitro* in lymphocytes. The groups studied consisted of 27 male dental laboratory technicians exposed to metal alloys (35–65% cobalt, 20–30% chromium, (0–30% nickel) in dental laboratories during the production of skeletal prostheses, and 15 male controls from the faculty of pharmacy. In the exposed group, a significant correlation was

found between urinary cobalt concentrations and frequencies of micronuclei in nasal cells, but not in lymphocytes. The results of multifactorial variance analysis revealed that occupational exposure was the only factor that significantly influenced the induction of micronuclei.

The possible genotoxic effects of occupational exposure to cobalt alone or to hard-metal dust was explored in a study using the in-vitro cytochalasin-B micronucleus test in lymphocytes as end-point for mutations (De Boeck et al., 2000). The authors concluded that workers exposed solely to cobalt-containing dust at TLV/TWA (20µg cobalt/g creatinine in urine, equivalent to TWA exposure to 20 µg/m3) did not show increased genotoxic effects but that workers who smoked and were exposed to hard-metal dusts form a specific occupational group which needs closer medical surveillance.

Hengstler et al. (2003) concluded from a study of workers co-exposed to cadmium, cobalt, lead and other heavy metals, that such mixed exposure may have genotoxic effects. The authors determined DNA single-strand break induction by the alkaline elution method in cryopreserved mononuclear blood cells of 78 individuals co-exposed to cadmium (range of concentrations in air, 0.05–138 µg/m3), cobalt (range, 0–10 µg/m3) and lead (range, 0–125 µg/m3) and of 22 subjects without occupational exposure to heavy metals (control group). Some concerns about the study were addressed by Kirsch-Volders and Lison (2003) who concluded that it did not provide convincing evidence to support the alarming conclusion of Hengstler et al. (2003).

1.7.4 Summary and discussion of mutagenicity

Data regarding the genotoxic effects specifically for cobalt(II) diacetate and it its hydrate form are very limited. However, the results of genotoxicity assays with a variety of cobalt(II) salts demonstrate the mutagenic potential of these salts both *in vitro* and *in vivo*. Cobalt, in salts with a valence state of +2, was mostly negative in mutagenicity tests conducted in *Salmonella typhimurium*, *Escherichia coli*, and yeast, but weakly positive in *Bacillus subtilis.* In mammalian test systems, many cobalt compounds and metals are genotoxic. Cobalt compounds and cobalt metals have been reported to cause clastogenic effects in mammalian cells such as human lymphocytes, transformation in hamster cells, sister chromatid exchanges in human lymphocytes, and micronucleus formation in mouse bone marrow cells and human lymphocytes. It has also been demonstrated to induce micronuclei in vivo (bone marrow in mice).

TC-C&L concluded on the then available data after discussions in November 2003, May 2004 and September 2004 that cobalt(II) diacetate[8] and cobalt(II) diacetate tetrahydrate should be classified with R68 (summary record ECBI/139/04 rev.2).

[8] The EC number 200-755-8 and CAS number 71-48-7 specified in Annex VI refer to the substance where cobalt acetate has the oxidation state +2.

1.8 Carcinogenicity

1.8.1 Non-human information

1.8.1.1 Carcinogenicity: oral

No carcinogenicity studies were available using the oral route of exposure.

1.8.1.2 Carcinogenicity: inhalation

No carcinogenicity studies were available specifically to cobalt di(acetate) and its hydrates using the inhalation route of exposure. However, inhalation exposure studies with animals have been performed with a comparable cobalt(II) salt (see section 1.8.3.1).

1.8.1.3 Carcinogenicity: dermal

No carcinogenic studies were available using the dermal route of exposure.

1.8.2 Human information

No studies are available specifically to cobalt di(acetate) and its hydrates in humans.

1.8.3 Other relevant information

1.8.3.1 In vivo data

Inhalation exposure studies with animals have been performed with other comparable cobalt compounds. The NTP (1998) conducted a two year inhalation carcinogenicity study of cobalt sulphate heptahydrate (a soluble cobalt salt) with mice and rats. These studies and results are summarized below.

The following information was taken from the RoC Background Document for Cobalt Sulphate, for Cobalt, published in 2002.

NTP carcinogenicity bioassay in mice

Groups of six-week-old B6C3F1 mice (50 of each sex) were administered cobalt sulphate heptahydrate aerosols by inhalation at target concentrations of 0, 0.3, 1.0, or 3.0 mg/m^3, 6 h/day, 3 days/week, for 105 weeks (NTP 1998, Bucher *et al.* 1999[9]). The corresponding concentrations expressed as elemental cobalt were 0, 0.063 mg/m^3, 0.210 mg/m^3, and 0.628 mg/m3. Exposure concentrations were based on previous subacute and subchronic studies (Bucher *et al.* 1990, NTP 1991). Cobalt sulphate heptahydrate was generated and delivered from an aqueous solution via a compressed-air-driven nebulizer, an aerosol charge neutralizer, and an aerosol distribution system.

[9] It should be noted that the article referring to, *Bucher et al. 1999*, reports the test substance to be cobalt sulphate hexahydrate.

The aerosol was dried and mixed with humidified air before delivery to the inhalation chambers, thus allowing partial rehydration of the aerosol particles. The mass median aerosol particle diameter was 1 to 3 μm, and the aerosol consisted of 1 mole of cobalt, 1 mole of sulfate, and 5.9 moles of water per mole of aerosolized cobalt sulphate (Bucher *et al.* 1999). The overall chemical purity of the study material was reported to be 99%. Survival was not significantly affected by exposure. Mean body weights were slightly higher in exposed females than in controls, and mean body weights were lower in the high-dose males than in controls from week 96 to the end of the study.

The incidences of alveolar/bronchiolar adenoma, alveolar/bronchiolar carcinoma, and alveolar/bronchiolar adenoma or carcinoma (combined) showed a positive exposure response trend in all groups. The incidences of these neoplasms were significantly higher in all the high-dose groups than in the controls, as was the incidence of adenoma or carcinoma (combined) in mid-dose female mice. The NTP (1998) concluded that there was clear evidence of carcinogenic activity in both male and female mice, based on increased incidences of lung tumors. Although the incidence of hemangiosarcoma was significantly increased in male mice in the mid-dose group, *Helicobacter hepaticus* infection was present in these mice, making interpretation of this finding difficult. Liver sections from several male mice were positive for bacteria, and the spectrum of liver lesions in these mice was consistent with *H. hepaticus* infection.

In addition to the neoplastic lesions, exposure to cobalt sulphate induced a spectrum of inflammatory, fibrotic, and proliferative lesions in other portions of the respiratory tract that were consistent with results observed in the shorter-term studies . These included hyperplasia of the olfactory epithelium (high-dose groups), squamous metaplasia of the larynx (all exposed groups), cytoplasmic vacuolization of the bronchi (all exposed groups), diffuse histiocytic cell infiltration (high-dose males), and focal histiocytic cell infiltration of the lung (high-dose females). Histiocytic infiltration was observed most often in lungs with alveolar/bronchiolar neoplasms and was attributed to the neoplasms, rather than to a direct effect of cobalt sulphate.

<u>NTP carcinogenicity bioassay in rats</u>

Groups of six-week-old F344/N rats (50 of each sex) were administered cobalt sulphate heptahydrate aerosols by inhalation at target concentrations of 0, 0.3, 1.0, or 3.0 mg/m^3, 6 h/day, 5 days/week, for 105 weeks (NTP 1998, Bucher *et al.* 1999). Exposure concentrations were based on previous subacute and subchronic studies (Bucher *et al.*1990, NTP 1991). Survival of exposed rats did not differ significantly from that of controls. Among males, survival was 34%, 30%, 42%, and 30% in the control, low exposure, mid-exposure, and high-exposure groups, respectively. Overall, survival was higher in females than in males, at 56%, 51%, 52%, and 60% in the control, low exposure, mid-exposure, and high-exposure groups, respectively. Mean body weights in all exposed groups did not differ significantly from those of controls throughout the study). The incidence of alveolar/bronchiolar adenoma or carcinoma (combined) showed a significant positive exposure-related trend in male rats and was significantly higher in the high-dose group than in the control group. A significant positive exposure-related trend for alveolar adenoma, carcinoma, and adenoma or carcinoma (combined) was observed in female rats, and incidences were significantly higher in the mid-dose and high-dose groups than in the controls. In addition, squamous-cell carcinoma of the lung was observed in two female rats (one each in the mid-dose and high-dose groups). The incidence of benign adrenal pheochromocytoma was increased in high-dose females, and the incidence of benign, complex, or malignant pheochromocytoma (combined) was increased in mid-dose males and high-dose females. The increased incidences in the high-dose females were considered to be exposure related. The NTP (1998) concluded that there was some evidence of carcinogenicity in male rats, based on increased incidences of alveolar/bronchiolar neoplasms. Marginal increases in adrenal medullary tumors in male rats may have been related to exposure to

cobalt sulphate heptahydrate. There was clear evidence of carcinogenicity in female rats, based on increased incidences of alveolar/bronchiolar neoplasms and pheochromocytoma of the adrenal medulla.

Nonneoplastic lesions of the respiratory tract generally were more severe in rats than in mice. Significantly increased incidences of inflammatory, fibrotic, and proliferative lesions were observed in all dose groups in the lung (hyperplasia and metaplasia of the alveolar epithelium, granulomatous inflammation, interstitial fibrosis, and proteinosis), nose (lateral wall hyperplasia and olfactory epithelium atrophy), and larynx (squamous metaplasia of the epiglottis). The NTP characterized all fibroproliferative lesions as atypical hyperplasia. Several animals had malignant neoplasms with a very prominent fibrous component, some of which presumably had progressed from atypical hyperplasia. The NTP (1998) concluded that it was clear that all the morphologic variants of proliferative lesions represented a response to cobalt sulphate heptahydrate.

Summary of NTP carcinogenicity in mice and rats
Under the conditions of these 2-year inhalation studies there was some evidence of carcinogenicity of cobalt sulphate in male F344/N rats based on increase incidences of alveolar/bronchiolar neoplasms. Marginal increase of pheochromocytomas of the adrenal medulla may have been related to exposure to cobalt sulphate heptahydrate. There was clear evidence of the carcinogenic activity in female F344/N rats based on incidences of alveolar/bronchiolar neoplasms and pheochromocytomas of the adrenal medulla in groups exposed to cobalt sulphate heptahydrate. There was clear evidence of carcinogenic activity of cobalt sulphate heptahydrate in male and female B6C3f1 mice base on increase incidences of alveolar/bronchiolar neoplasms.

Other animal studies
Syrian golden hamsters (51 per group) exposed by inhalation (as cobalt oxide) at 10.0 mg/m^3 for 7h/day, 5 days/week, for a lifetime developed emphysema, but the incidence of pulmonary tumors was not different from controls. While tobacco smoke exposure induced pulmonary tumors in 14/51 animals, the incidence in animals exposed to both tobacco smoke and cobalt oxide was 11/51 (Wehner et al., 1977).

Different forms of cobalt (pieces, powder, alloy particles, soluble and insoluble salts) have been investigated for possible carcinogenic effects in long-term animal experiments with rabbits, rats, mice, hamster and guinea-pigs. Several routes of administration of the compound have been used, but mainly intramuscular injections (Jensen A.A, & Tüchsen, F., 1990). See Annex II for a summary of the results.

1.8.3.2 Human data

Several epidemiological studies addressing cancer risk in the hard-metal and cobalt production industry have been reported.

The following information was taken from the RoC Background Document for Cobalt Sulphate, for Cobalt, published in 2002.

Hard-metal industry
Four mortality studies of the hard-metal industry have been conducted in Sweden and France. Most of these studies investigated the effects of occupational exposure to hard metals (cobalt and tungsten) or metallic cobalt. (Hogstedt *et al.* 2000, Lasfargues *et al.* 1994, Moulin *et al.* 1998, Wild

et al. 2000; reported in IARC 2006). These studies have reported increases in lung cancer from occupational inhalation exposure to hard metal.

Hogstedt & Alexandersson (1990) reported on 3163 male workers, each with at least 1 year of occupational exposure at hard metal manufacturing plants in Sweden during 1940–1982 and followed from 1951 to 1982. Exposures included a number of other substances used in the production of hard metal, such as tungsten carbide. The lung cancer SMR was 1.34 (95% CI = 0.77–2.13); the all-cause mortality SMR was slightly less than unity. Among workers with more than 10 years of employment and more than 20 years since first exposure, a significant excess of lung cancer mortality was observed (SMR = 2.78, 95% CI = 1.11–5.72). Smoking habits among hard metal workers were reported to be similar to those of the male Swedish population.

Lasfargues et al. (1994) conducted a cohort mortality study of 709 male workers employed for ≥1 year at a hard metal manufacturing plant (including two workshops) in central France. Follow-up was from 1956 to 1989. Categories of exposure were defined based on dust and urinary measurements of cobalt taken in 1983. Workers who had been employed in jobs with different degrees of exposure were categorized according to their highest exposure. Job histories were obtained from company records; before 1970, however, the records were often missing. The overall mortality did not differ from expected (SMR = 1.05, 95% CI = 0.82–1.31). Mortality due to lung cancer was in excess (SMR = 2.13, 95% CI = 1.02–3.93), and the excess was highest among workers in the areas with highest exposures to cobalt (SMR = 5.03, 95% CI = 1.85–10.95).

An industry-wide cohort mortality study of the French hard metal industry was conducted by Moulin et al. (1998) to further evaluate the potential association of lung cancer risk with occupational exposure to cobalt and tungsten carbide. The cohort included 5777 men and 1682 women (total = 7459 workers) from 10 factories (most of which were in eastern France), including the factory studied by Lasfargues et al. (1994). The all-cause mortality SMR was 0.93; the lung cancer SMR was 1.30 (95% CI = 1.00–1.66). Sixty-one of the 63 lung cancer deaths in the cohort were included in a nested case–control study. Three controls that were alive on the date the case died were matched to each case based on gender and age. Occupational exposure of the cases and controls was evaluated based on a job–exposure matrix involving 320 job periods and exposure intensity scores from 0 to 9. Data on smoking were available for 80% of the cases and controls. The odds ratio for workers exposed to cobalt and tungsten carbide was 1.93 (95% CI = 1.03–3.62) for exposure levels 2–9 versus levels 0–1. The odds ratio for cobalt with tungsten carbide increased with duration of exposure and cumulative dose, but less so for level of exposure. Adjustments for exposure to known or suspected carcinogens and smoking did not change the results.

A study of the largest plant in the multicentre cohort of Moulin et al. (1998) was conducted by Wild et al. (2000). The authors used the same job–exposure matrix of Moulin et al. (1998) but made use of the more detailed job histories available. Follow-up was from 1968 to 1992. The SMR for the all-cause mortality was 1.02 (95% CI = 0.92–1.13). The SMR for lung cancer among men was increased (SMR = 1.70, 95% CI = 1.24–2.26). The lung cancer SMR for exposure to hard metal dust at an intensity score of ≥2 was 2.02 (95% CI = 1.32–2.96). In a Poisson regression model including terms for smoking and other occupational carcinogens, the risk for lung cancer increased with duration of exposure to cobalt with tungsten before sintering; there was no evidence of risk from exposure to sintered hard metal dust.

Cobalt production industry

Moulin et al. (1993) studied the mortality of a cohort of 1148 workers in a cobalt electrochemical plant in France that produced cobalt and sodium by electrochemistry, extending the follow-up of an earlier study by Mur et al. (1987; reported in IARC 1991). The cohort included all men who had

worked at the plant for a minimum of 1 year between 1950 and 1980. Follow-up was to the end of 1988 and was obtained for 99% of French-born workers. Because of difficulty in follow-up of non-French workers, results were presented only for the 870 French-born (i.e. a loss to follow-up of 24%). The SMR for all causes of death was 0.95 (95% CI = 0.78–1.26). The SMR for lung cancer was 1.16 (95% CI = 0.24–3.40) among workers exclusively employed in cobalt production and 1.18 (95% CI = 0.32–3.03) for workers ever employed in cobalt production.

Other cobalt compounds

Tüchsen et al. (1996) did not find evidence of an increased risk of lung cancer among a cohort of 874 women occupationally exposed to poorly soluble cobalt–aluminate spinel in two porcelain production factories in Denmark compared with that expected based on national rates for Danish women.

Summary on human data

Available studies of the carcinogenic effects of cobalt in occupationally-exposed humans have reported mixed results, with both positive and negative results.

Several studies of hard metals (cobalt and tungsten carbide) exposure to humans (Lasfargues et al. 1994; Moulin et al. 1998; Wild et al. 2000) have reported increases in lung cancer from occupational inhalation exposure to hard metal (ASTDR, 2004). Even thought these studies consistently reported an increased risk of lung cancer among workers exposed to cobalt, the workers were also exposed to other agents (e.g., tungsten carbide) and probably were not exposed to soluble cobalt (Report on Carcinogens, 2004). Thus, it is difficult to ascertain whether the increased incidence of lung cancer is attributable to cobalt. Only one study investigated the effects of exposure to cobalt salts. The initial study reported an increased risk of lung cancer among cobalt production workers, but a follow-up study of the same workers found no increased risk of cancer (Mur et al. 1987, Moulin et al. 1993). Interpretation of this finding is limited by the small number of exposed workers who developed cancer.

The IARC in volume 52 (1991) reviewed the carcinogenic risk to humans of cobalt and cobalt compounds and concluded the evidence of carcinogenicity was *inadequate*

1.8.3.3 IARC assessments

The IARC has classified cobalt and cobalt compounds as possibly carcinogenic to humans (Group 2B) based on sufficient evidence that cobalt metal powder and cobaltous oxide are carcinogenic in animals (IARC, 1991). The IARC recently (2006) classified cobalt metal with tungsten carbide as probably carcinogenic to humans (Group 2A). Cobalt metal without tungsten carbide and cobalt sulphate and soluble cobalt(II) salts were classified as possibly carcinogenic to humans (Group 2B) (IARC, 2006). This was based on sufficient evidence in experimental animals for the carcinogenicity of cobalt sulphate and cobalt metal powder.

1.8.4 Summary and discussion of carcinogenicity

Lifetime inhalation of cobalt sulphate resulted in increased tumor incidences in both rats and mice; NTP reported that there was some evidence of carcinogenicity in male Fischer 344 (F344) strain rats, and clear evidence of carcinogenicity in female F344 strain rats and male and female B6C3F1 strain mice following inhalation exposure. Oral and dermal data on the carcinogenic effects of cobalt and cobalt compounds are not available.

TC-C&L concluded on the then available data after discussions in November 2003, May 2004 and September 2004 that cobalt(II) diacetate[10] and cobalt(II) diacetate tetrahydrate should be classified with R49 (summary record ECBI/139/04 rev.2).

1.9 Toxicity for reproduction

1.9.1 Effects on fertility

No fertility studies were available specifically to cobalt(II) diacetate and its hydrates. However, studies have been conducted with soluble cobalt compounds to explore their potential effect on fertility (see section 1.9.3.1).

1.9.1.1 Human information

No human studies were available specifically to cobalt(II) diacetate and its hydrates regarding fertility effects in humans. There is some information available however of human exposure to cobalt (as cobalt chloride) see section 5.9.4

1.9.2 Developmental toxicity

1.9.2.1 Non-human information

No developmental studies were available specifically to cobalt(II) diacetate and its hydrates. However, studies have been conducted with soluble cobalt compounds to explore their potential effect on development (see section 1.9.3.2).

1.9.2.2 Human information

No human studies were available specifically to cobalt(II) diacetate and its hydrates regarding developmental effects in humans. There is some information available however of human exposure to cobalt (as cobalt chloride) see section 1.9.3.3.

1.9.3 Other relevant information

1.9.3.1 Effects on fertility

Several studies have been conducted with soluble cobalt compounds to explore their potential effect on fertility.

[10] The EC number 200-755-8 and CAS number 71-48-7 specified in Annex VI refer to the substance where cobalt acetate has the oxidation state +2.

The following information was taken from the ASTDR Toxicological profile for cobalt, published in 2004.

In animals, long-term exposure to cobalt-containing aerosols has resulted in effects on reproductive end points. Testicular atrophy was reported in rats, but not in mice, exposed to 19 mg cobalt/m^3 as cobalt sulphate over 16 days (Bucher et al. 1990; NTP 1991). Following exposure of mice to cobalt (as cobalt sulphate) for 13 weeks, a decrease in sperm motility was found at 1.14 mg cobalt/m^3, and testicular atrophy was found at 11.4 mg cobalt/m^3. A significant increase in the length of the estrous cycle was reported in female mice exposed to 11.4 mg cobalt/m^3 for 13 weeks (Bucher et al. 1990; NTP 1991). No effects on the male or female reproductive systems were observed in rats similarly treated for 13 weeks (Bucher et al. 1990; NTP 1991), or in mice or rats exposed to up to 1.14 mg cobalt/m3 for 104 weeks (Bucher et al. 1999; NTP 1998).

Testicular degeneration and atrophy have been reported in rats exposed to 13.3–58.9 mg cobalt/kg/day as cobalt chloride for 2–3 months in the diet or drinking water (Corrier et al. 1985; Domingo et al. 1984; Mollenhauer et al. 1985; Nation et al. 1983; Pedigo and Vernon 1993; Pedigo et al. 1988), or in mice exposed to 43.4 mg cobalt/kg/day as cobalt chloride for 13 weeks in the drinking water (Anderson et al. 1992, 1993). Pedigo and Vernon (1993) reported that cobalt dichloride (400 ppm in drinking water for 10 weeks) increased pre-implantation losses per pregnant female in the dominant lethal assay by compromising the fertility of treated male mice.

Other publications
In an abstract reported by Elbetieha et al. (2004), sexually mature male mice exposed to cobalt(II) chloride at 200, 400, or 800 mg/l in their drinking-water for 12 weeks were assessed for effects on fertility by breeding these exposed males to unexposed females. Fertility, as measured by successful matings, was reduced in mice exposed to cobalt chloride at 400 and 800 mg/l (internal doses of 46.91 ± 4.78 and 93.01 ± 6.76 mg/kg body weight per day, respectively). The number of implantation sites was significantly reduced in females mated with exposed males at 400 and 800 mg/l. The number of viable fetuses was decreased in females mated with males at all three exposure levels. In the 800 mg/l males, absolute epididymal weight was significantly decreased, whereas relative and absolute testes weights were decreased in males exposed to both 400 and 800 mg/l. Epididymal sperm count was decreased in males of all three exposure levels. At 400 and 800 mg/l, males also exhibited reduced testicular sperm counts and daily sperm production. The testes displayed severe abnormalities, including hypertrophy of the interstitial Leydig cells, congested blood vessels, degeneration of the spermatogonial cells, and necrosis of seminiferous tubules and interstitial tissue.

1.9.3.2 Developmental toxicity

Several studies have been conducted with soluble cobalt compounds to explore their potential effect on development.

The following information was taken from the ASTDR Toxicological profile for cobalt, published in 2004.

Oral exposure of female rats to cobalt chloride at 5.4 or 21.8 mg cobalt/kg/day from gestation day 14 through lactation day 21 has been shown to result in stunted growth and decreased survival, respectively, of newborn pups (Domingo et al. 1985b). The effects on the offspring occurred at levels that also caused maternal toxicity (reduced body weight and food consumption, and altered hematological measurements) and might therefore have been an indirect effect of maternal toxicity

rather than a direct effect of cobalt on the fetus (Domingo et al. 1985b). Teratogenic effects were not observed.

Szakmary et al. (2001) reported that exposure of pregnant rats to 0–38 mg Co/kg-day as cobalt sulphate did not result in changes in fetal death rates, maternal body weigh gain, average litter size, or average fetal or placental weights; however, a dose-related trend was seen for the percent of fetuses with retarded body weights. In contrast, no effects on fetal growth or survival were found following exposure of rats to 24.8 mg cobalt/kg/day as cobalt chloride during gestation days 6–15 (Paternian et al. 1988). In mice, exposure to 81.7 mg cobalt/kg/day as cobalt chloride during gestation days 8–12 was reported to have no effect on fetal growth or mortality in mice (Seidenberg et al. 1986). In a later mouse study that exposed pregnant mice to 19 mg Co/kg-day as cobalt sulphate, no changes in litter size, postimplantation loss, or average fetal or placental weights were seen; the only difference seen was an increase in the percent of fetuses with retarded body weights (Szakmary et al. 2001). The same study reported that rabbits exposed to ≥ 38 mg Co/kg-day, as cobalt sulphate, showed nearly complete maternal lethality, and complete fetal loss. Rabbits exposed to 7.6 mg Co/kg, as cobalt sulphate, showed significant increases in mortality and fetal resorption, as well as an increase in fetuses with retarded body weight (Szakmary et al. 2001).

Other publications
Wide (1984) reported that a single intravenous injection of cobalt chloride hexahydrate into pregnant NMRI mice (5 mM per animal in the tail vein; [120 μg/animal]) on day 8 of gestation significantly affected fetal development (71% of skeletal malformations versus 30% in controls); in animals injected at day 3 of gestation, no interference with implantation was noted. In the same experiment but replacing cobalt chloride by tungstate (25 mM of W per animal; [460 μg/animal]) a significant increase in the number of resorptions was observed (19% versus 7% in controls), but no skeletal malformations (RoC, 2006).

Paksy et al. (1999) found that in-vitro incubation of postblastocyst mouse embryos with cobalt(II) ions (as cobalt sulphate) adversely affected the development stages at a concentration of 100 μM and decreased the trophoblast area (at a concentration of 10 μM) (ASDTR, 2004).

1.9.3.3 Human data

No developmental effects on human fetuses were observed following treatment of pregnant women with cobalt chloride to raise hematocrit and hemoglobin levels that are often depressed during pregnancy. Dosages up to 0.6 mg cobalt/kg/day for 90 days were given (Holly 1955). Examination of the fetuses, however, was limited to the reporting of obvious birth defects, and exposure only occurred in the final trimester (ASTDR, 2004).

1.9.4 Summary and discussion of reproductive toxicity

No studies with Cobalt diacetate are available. Mice and rats exposed to high oral doses of cobalt dichloride for 2-3 months experienced testicular degeneration and atrophy and reduced fertility. Stunted growth and decreased survival were observed among newborn rats at dose levels that also caused maternal toxicity in one study. Similar doses did not produce such effects in another study of rats or in a study of mice. Rabbits exposed at high doses were found to have increased mortality, fetal resorption, and number of fetuses with decreased body weight. No teratogenic effects were reported in any of the studies.

TC-C&L concluded on the then available data after discussions in November 2003, May 2004 and September 2004 that cobalt(II) diacetate[11] and cobalt(II) diacetate tetrahydrate should be classified with R60 (summary record ECBI/139/04 rev.2).

1.10 Other effects

Not relevant for this type of dossier.

[11] The EC number 200-755-8 and CAS number 71-48-7 specified in Annex VI refer to the substance where cobalt acetate has the oxidation state +2.

2 ANNEX II. ANIMAL CARCINOGENICITY AND RELATED EFFECTS DATA OF COBALT COMPOUNDS.

Reference	Species/ Strain	Sex	Dose Schedule	Experimental parameter/observation	Group 0	1	2	3	Comments
Cobalt metal powder									
Heath (1954a, 1956)	Rat Hooded	M F	i.m. single inj. fowl serum	Dose (mg) Survival (122 weeks) Local sarcoma Dose (mg) Survival (122 weeks) Local sarcoma	0 Not given 0/10 0 Not given 0/10	28 28 5/10	 28 8/10		
Health & Daniel (1962)	Rat Hooded	F	intrathoracic in serum	Dose (mg) Survival (3 days) Thoracic tumour	0	28 12/20 4/12			
Jasmin & Riopelle (1976)	Rat Sprague-Dawley	F	intrarenal	Dose (mg) Survival (12 months) Kidney tumour	0 Not given 0/16	5 0/18			Inadequate
Cobalt alloys									
Heath *et al*. (1971); Swanson *et al*. (1973)	Rat Hooded	F	i.m. single inj., wear particles from Co/Cr/Mo in horse serum	Dose (mg) Survival (29 months) Local sarcoma	0 Not given	28 23/80			
Gaechter *et al*. (1977)	Rat Sprague-Dawley	M+F	i.m. impl. Co/Cr/W/Ni/C/Mn/Si/Fe (1.6 x 8 mm)	Dose (polished rod) Survival (2 years) Local tumour	0[a] Not given 0/30	0[a] 0/30	1 0/90		Not significant difference in distant tumours
Memoli *et al*. (1986)	Rat Sprague-Dawley	M+F	Intraoss. impl., Co/Cr/Ni/Mo/W/Zr	Dose (powder, wire, rod) Survival (30 months) Local sarcoma	0[a] Not given 0/51	0[a] 0/26	1 7/76[b]		
Memoli *et al*. (1960)	Rat Wister	M+F	s.c. impl. Co/Cr/Mo/Ni	Dose (pellets-2mm diam) Survival (27 months) Local sarcoma	 Not given	 0/10			
Cobalt alloys (contd)									

Reference	Species/ Strain	Sex	Dose Schedule	Experimental parameter/observation	Group 0	Group 1	Group 2	Group 3	Comments
Meachim *et al*. (1982)	Rat Wistar and hooded	F	i.m. impl. Co/Cr/Mo fine and coarse particles	Dose (mg) Survival (2 years) Local tumour	0 5/50 0	28 11/51 0	28 7/61 0	28 0/53 0	
Steinhoff &Mohr (1991)	Rat Sprague-Dawley	M+F	3 i.p ijn., Co/Al/Cr spinel powder	Dose (mg/kg bw) Survival (2 years) Local tumour	0 Not given 1/20	200 2/20			
Steinhoff &Mohr (1991)	Rat Sprague-Dawley	M+F	Intratracheal inst. 1 x 2 weeks Co/Al/Cr spinel 2 years	Dose (mg/kg bw) Survival (2 years) Squamous-cell tumour of the lung	0 Not given 0/200	10 3/100			
Meachim *et al*. (1982)	Guinea-pig	F	i.m. impl. Co/Cr/Mo powder	Dose (mg) Survival (3 years) Local tumour Local fibroblastis hyperplasia		28 12/46 0/46 8/46			
Cobalt[II] oxide									
Gilman & Ruckerbuaer (1962)	Mouse Swiss	F	i.m. inj., in each thigh	Dose (mg/site) Survival (13 weeks) Local tumour sarcoma	0 48/51 0/48	10 46/75 0/46			
Steinhoff &Mohr (1991)	Rat Sprague-Dawley	M	Intratracheal inst. 1 x 2 weeks 2 years	Dose (mg/kg bw) Survival (2 years) Benign squamous pulmonary tumour Bronchiolalveolar adenoma Pulmonary adenocarcinoma Bronchalveolar adenocarcinoma	0 Not given 0/100 0/100 0/100 0/100	2 1/50 0/50 0/50 0/50	10 0/50 2/50 2/50 1/50		
		F		Dose (mg/kg bw) Survival (2 years) Bronchiolalveolar adenoma Bronchalveolar adenocarcinoma	0 Not given 0/100 0/100	2 1/50 0/50	10 0/50 1/50		
Gilman & Ruckerbuaer (1962)	Rat Wistar	M+F	i.m. inj.	Dose (mg/site) Survival (90 days) Local sarcoma	0 10/10 0/10	30 10/10 5/10			
Gilman (1962)	Rat Wistar	M+F	i.m. inj.	Dose (mg/site) Survival (13 weeks) Local sarcoma		20 24/32 13/29 sites			
Cobalt[II] oxide (contd)									
Steinhoff &Mohr (1991)	Rat	M	s.c. inj.	Dose (mg/kg bw)	0	2	10		

Reference	Species/ Strain	Sex	Dose Schedule	Experimental parameter/observation	Group				Comments
					0	1	2	3	
	Sprague-Dawley		2 mg/kg bw 5/weeks or 10 mg/kg bw 1/week for 2 years	Survival (2 years) Local malignant tumour	Not given 0/20	 5/10	 4/10		
Steinhoff &Mohr (1991)	Rat Sprague-Dawley	M+F	3 i.p. inj. at 2-month intervals	Total dose (mg/kg bw) Survival (2 years) Local malignant tumour	0 Not given 1/20	200 14/20			
Wehner *et al.* (1977)	Hamster ENG:ELA	M	Inhalation 7h/day 5d/week for life	Dose (mg/m^3) Survival (18 months) Reticulum-cell sarcoma Carcinoma Lymphosarcoma Leukaemia Plasma cell tumour	0 7/51 0/51 0/51 0/51 0/51 1/51	200 9/51 1/51 1/51 0/51 0/51 0/51			No statistical difference
Cobalt [II] sulphide									
Gilman (1962)	Rat Wistar	M+F	i.m. inj.	Dose (mg/site) Survival (13 weeks) Local sarcoma		20 29/30 35/58 sites			
Jasmin & Riopelle (1976)	Rat Sprague-Dawley	F	intrarenal	Dose (mg) Survival (12 months) Kidney tumour	0 Not given 0/16	5 0/20			Inadequate
Cobalt[II] chloride									
Shabaan *et al.* (1977)	Rat Wistar	M	s.c. 2 x 5 day, 9-d interval	Dose (mg/kg bw) Survival[c] Subcutaneous sarcoma	0 19/20 0/19	40 11/20 8/11	40 16/20 6/16		 $p < 0.001$ (Fisher exact test)
Cobalt naphthenate									
Nowak (1966)	Mouse NS	NS	i.m. inj. NS	Dose (mg) Survival Tumour of the striated muscle	0	0.2 8/30			Inadequate
Nowak (1961)	Rabbit	M	i.m. i.v. i. pleural i. hepatic	Dose unspecified	0	5 1 1 1			Inadequate
Cobalt [III] acetate									
Stoner *et al.* (1976)	Mouse	M+F	i.p. inj.	Total dose (mg/kg bw)	0	95	237	475	Not significant

Reference	Species/ Strain	Sex	Dose Schedule	Experimental parameter/observation	Group				Comments
					0	1	2	3	
	Strain A		3/week, 24 doses	Survival (30 weeks) Pulmonary tumour	19/20 7/19	20/20 8/20	20/20 8/20	17/20 10/17	

[a]group 0, untreated; group 1, sham-treated; [b]Powder, 1/18 sarcoma; MP35N, 3/26 sarcomas; compacted wire, 3/32 sarcomas; [c]2 months for groups 0 and 1; at 8 months for group 2; NS, not specified.
i.m., intramuscular; inj, injection; impl., implantation; intraoss, intra-osseous; s.c., subcutaneous; inst., instillation; i.p., intraperitoneally, i.v., intravenous