DISPOSITION OF PEER REVIEW COMMENTS FOR TOXICOLOGICAL PROFILE FOR COBALT

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Agency for Toxic Substances and Disease Registry

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Peer reviewers for the third pre-public draft of the Toxicological Profile for Cobalt were:

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NOTE: Peer reviewer comments are written next to "COMMENTS:" in unformatted text. Any italicized text following the comment is added for clarification purposes. Any page and line numbers that were added by the Reviewers have been kept, but often will not align with the appropriate text.

Comments provided by Peer Reviewer #1

ATSDR Charge Questions and Responses

Chapter 1. Relevance to Public Health

QUESTION: Do you agree with those effects known to occur in humans as reported in the text? If not, please explain why and provide a copy of additional references you would cite and indicate where (in the text) these references should be included.

COMMENT: Yes, I agree with the exception of the lack of nephrotoxicity. See text and attached summary for full details.

RESPONSE: *No response needed.*

QUESTION: Are the effects only observed in animals likely to be of concern to humans? Why or why not? If you do not agree, please explain.

COMMENT: Yes, I think they would also be a concern to humans. Inhalation studies with metal-based particulate matter (PM) are largely translatable to humans, and therefore relevant to the text.

RESPONSE: *No response needed.*

QUESTION: Have exposure conditions been adequately described? If you disagree, please explain

COMMENT: Yes, exposure has been adequately described.

RESPONSE: *No response needed.*

Minimum Risk Levels (MRLs)

QUESTION: If no MRLs have been derived, do you agree that the data do not support such a derivation? Please explain.

COMMENT: I agree with what has been written.

RESPONSE: *No response needed.*

QUESTION: If MRLs have been derived, do you agree with the proposed MRL values? Explain. If you disagree, please specify the MRL value that you would propose.

COMMENT: Yes, I agree.

RESPONSE: *No response needed.*

QUESTION (Subset of preceding question): Do you agree/disagree with each component of the total uncertainty factor? Explain. If you disagree, please specify the uncertainty factor(s) that you propose.

COMMENT: Yes, I agree.

RESPONSE: *No response needed.*

QUESTION (Subset of preceding question): Please comment on any aspect of our MRL database assessment that you feel should be addressed.

COMMENT: N/A

RESPONSE: *No response needed.*

Chapter 2. Health Effects

QUESTION: Do the health effect conclusions made in Chapter 2 adequately reflect the findings in the published literature? If not, please suggest appropriate changes.

COMMENT: Yes

RESPONSE: *No response needed.*

QUESTION: Were adequately designed human studies identified in the text (i.e., good exposure data, sufficiently long period of exposure to account for observed health effects, adequate control for confounding factors)? Were the major study limitations sufficiently described in the text without going into lengthy discussions? If study limitations were not adequately addressed, please suggest appropriate changes.

COMMENT: Yes, I would agree with these statements.

RESPONSE: *No response needed.*

QUESTION: Were adequately designed animal studies identified in the text (i.e., adequate number of animals, good animal care, accounting for competing causes of death, sufficient number of dose groups, and sufficient magnitude of dose levels)? If not, does the inadequate design negate the utility of the study? Please explain.

COMMENT: All animal studies cited were from peer-reviewed journals with acceptable numbers per treatment group.

RESPONSE: *No response needed.*

QUESTION: Were the animal species appropriate for the most significant toxicological endpoint of the study? If not, which animal species would be more appropriate and why?

COMMENT: Animal studies described were primarily rodents and hamsters, which are typical models for metals exposures (such as Co).

RESPONSE: *No response needed.*

QUESTION: Has adequate attention been paid to dose-response relationships for both human and animal data? Please explain.

COMMENT: Yes

RESPONSE: *No response needed.*

QUESTION: Are you aware of any studies that are not included in the profile that may be important in evaluating the toxicity of the substance? Please provide a copy of each study and indicate where in the text each study should be included.

COMMENT: Additional studies have been detailed in the text for citation.

RESPONSE: *Study by Tvermoes et al. (2014) has been included in the profile as requested by the reviewer. The following sentence has been added "Tvermoes et al. (2014) found no significant changes in hematological parameters following a 90-day exposure to cobalt in 10 volunteers.".*

QUESTION: Are you aware of any studies that are not included in the profile that may be relevant to deriving MRLs for any of the substance isomers? Please provide a copy if this is a new reference.

COMMENT: No

RESPONSE: *No response needed.*

QUESTION: Were all appropriate NOAELs and/or LOAELs identified for each study (both in the text and the Levels of Significant Exposure (LSE) tables and figures)? If not, did the text provide adequate justification for excluding NOAELs/LOAELs including, but not limited to, citing study limitations? Please suggest appropriate changes.

COMMENT: This was adequately addressed.

RESPONSE: *No response needed.*

QUESTION: Do you agree with the categorization of "less serious" or "serious" for the effects cited in the LSE tables? If not, please explain why and suggest appropriate changes.

COMMENT: Yes**.**

RESPONSE: *No response needed.*

QUESTION: Have all possible mechanisms of action been discussed within their relevant health effect section? If not, please explain. If citing a new reference, please provide a copy and indicate where (in the text) it should be included.

COMMENT: Yes, everything has been detailed.

RESPONSE: *No response needed.*

QUESTION: Are the conclusions appropriate given the overall database? If not, please discuss your own conclusions based on the data provided and other data provided to you but not presented in the text.

COMMENT: Overall the conclusions are appropriate.

RESPONSE: *No response needed.*

QUESTION: RADIOACTIVE COBALT STUDIES: Are you aware of any studies using radioactive cobalt isotopes that would improve the information presented in this chapter.

COMMENT: No.

RESPONSE: *No response needed.*

QUESTION: NANOPARTICLES: Is the section regarding cobalt nanoparticles appropriately detailed and accurate? If not, please identify its shortcomings, recommend topics to include, identify where those topics should be addressed in the text, and provide copies of the new references supporting those topics.

COMMENT: This section is detailed and accurate.

RESPONSE: *No response needed.*

Chapter 3. Toxicokinetics, Susceptible Populations, Biomarkers, Chemical Interactions

QUESTION: Is there adequate discussion of absorption, distribution, metabolism, and excretion of the substance? If not, suggest ways to improve the text.

COMMENT: Yes, this is adequate.

RESPONSE: *No response needed.*

QUESTION: Have all available pharmacokinetic/pharmacodynamic models and supporting data been presented? If not, please explain.

COMMENT: Yes, this has been presented.

RESPONSE: *No response needed.*

QUESTION: Is there adequate discussion of the differences in toxicokinetics between humans and animals? Is there adequate discussion of the relevance of animal toxicokinetic information for humans?

COMMENT: Yes, this is adequate.

RESPONSE: *No response needed.*

QUESTION: Are there any data relevant to child health and developmental effects that have not been discussed in the profile and should be? Please provide any relevant references.

COMMENT: No, what is written is adequate.

RESPONSE: *No response needed.*

QUESTION: Is there a discussion of populations at higher risk of susceptibility? Do you agree with the choice of populations? Please explain and provide any additional relevant references.

COMMENT: I agree with the choice of populations -this section is adequate.

RESPONSE: *No response needed.*

QUESTION: Are the biomarkers of exposure specific for the substance? Please explain.

COMMENT: Yes

RESPONSE: *No response needed.*

QUESTION: Are the biomarkers of effect specific for the substance? Please explain.

COMMENT: Yes, there's a discussion regarding exhaled breath condensate and urinary biomarkers.

RESPONSE: *No response needed.*

QUESTION: Is there adequate discussion of the interactive effects with other substances? Does the discussion concentrate on those effects that might occur at hazardous waste sites? Please explain and provide any additional references.

COMMENT: Yes, please see the document for full recommendations.

RESPONSE: *Recommendations from Reviewer#1 are detailed in* ***Comments from Summary Report-Reviewer 1Annotated*** *and* ***Annotated Comments on the Profile- Reviewer 1*** *sections below.*

QUESTION: If interactive effects with other substances are known, does the text discuss the mechanisms of these interactions? Please explain and provide any additional references.

COMMENT: *None provided.*

RESPONSE: *No response needed.*

Chapter 4. Chemical and Physical Information

QUESTION: Are any of the values or information provided in the chemical and physical properties tables wrong or missing? Please explain and provide any additional references.

COMMENT: This looks complete.

RESPONSE: *No response needed.*

QUESTION: Is information provided on the various forms of the substance? Please explain.

COMMENT: Yes, several compounds with Co have been addressed.

RESPONSE: *No response needed.*

Chapter 5. Potential for Human Exposure

QUESTION: Is the information on production, import/export, use, and disposal of the substance complete? Please explain and provide any additional relevant references.

COMMENT: This was well-done. Any additional citations have been directly mentioned in the tracked-changes version of the document.

RESPONSE: *The peer reviewer suggested adding citations in the summary section in Chapter 5, where citations are not included as per ATSDR guidelines stated in the ATSDR guidelines "Guidance for the Preparation of Toxicological Profiles". Citations have been included in the relevant sections in Chapter 5. The reviewer did not suggest any new references.*

QUESTION: Has the text appropriately traced the substance from its point of release to the environment until it reaches the receptor population? Does the text provide sufficient and technically sound information regarding the extent of occurrence at NPL sites? Do you know of other relevant information? Please provide references for added information.

COMMENT: Yes, this section is appropriate and sufficient.

RESPONSE: *No response needed.*

QUESTION: Does the text cover pertinent information relative to transport, partitioning, transformation, and degradation of the substance in all media? Do you know of other relevant information? Please provide references for added information.

COMMENT: Yes, this section is appropriate and sufficient.

RESPONSE: *No response needed.*

QUESTION: Does the text provide information on levels monitored or estimated in the environment, including background levels? Are proper units used for each medium? Does the information include the form of the substance measured? Is there an adequate discussion of the quality of the information? Do you know of other relevant information? Please provide references for added information.

COMMENT: Yes, this section is appropriate and sufficient.

RESPONSE: *No response needed.*

QUESTION: Does the text describe sources and pathways of exposure for the general population and occupations involved in the handling of the substance, as well as populations with potentially high exposures? Do you agree with the selection of these populations? If not, why? Which additional populations should be included in this section?

COMMENT: Yes, this section is appropriate and sufficient.

RESPONSE: *No response needed.*

Chapter 6. Adequacy of the Database

QUESTION: Do you know of other studies that may fill a data gap? Please provide any relevant references.

COMMENT: No.

RESPONSE: *No response needed.*

QUESTION: Do you agree with the identified data needs? Please explain.

COMMENT: Yes.

RESPONSE: *No response needed.*

QUESTION: Are the data needs presented in a neutral, non-judgmental fashion? Please note any bias in the text.

COMMENT: Yes, they are relatively unbiased

RESPONSE: *No response needed.*

Chapter 7. Regulations and Guidelines

QUESTION: Are you aware of any additional regulations or guidelines that should be included? Please provide citations.

COMMENT: No, I am not aware of any additional to be included.

RESPONSE: *No response needed.*

QUESTION: Are there any that should be removed? Please explain.

COMMENT: No, there are none that should be removed.

RESPONSE: *No response needed.*

Additional References from Reviewer*

**These are references cited within the reviewer's individual comments. Responses to the reviewer's comments specify the disposition of these references within the toxicological profile.*

Appendices

QUESTION: Please provide any comments on the content, presentation, etc. of the included appendices.

COMMENT: *None provided.*

RESPONSE: *No response needed.*

Comments from Summary Report- Reviewer 1

COMMENT: <u>Chapter 1. Relevance to Public Health</u>

- Major issues: My major issue with this chapter are the lack of citations provided. Several statements are made, but limited evidence is provided. This has been directly notated using the tracked-changes feature.
- No evidence or mention of nephrological/kidney toxicity, even though that tends to be a key target organ for metals exposures.
- Minor: revisions to oral cobalt ingestion, as mentioned in the document
- Define timeframes such as chronic, acute, upfront in the first chapter

RESPONSE*:*

- As per ATSDR guidelines detailed in "Guidance for the Preparation of Toxicological Profiles" citations are not included in Chapter 1.

- Health effects caused by exposure to cobalt included this Chapter are based on the most sensitive health effect endpoints that were evaluated in the systematic review in Appendix C. This profile is specific to cobalt. Additionally, the toxicity effects in kidney occurred at oral doses higher than humans would be exposed to.

- Updated to include definitions.

- Minor in text and editorial comments have been included in the profile.

COMMENT: Chapter 2. Health Effects

- Can you include intratracheal or intranasal instillation of nanoparticles?
- No other major comments

***RESPONSE**: No changes were made. The ToxProfile focuses on the primary routes of exposure (oral, inhalation, and dermal) primarily.*

COMMENT: Chapter 3. Toxicokinetics, Susceptible Populations, Biomarkers, Chemical Interactions

- Toxicokinetic description is not necessarily specific to Co. I think I would mention that inhaled particles all act in a similar manner.
- Issues with citations throughout. Please check citations.

Be consistent with abbreviations

***RESPONSE**:*

-Although the deposition of particles is relatively independent of the substance, the toxicity thereafter is substance specific.

- Updated and fixed citations where appropriate.

COMMENT: Chapter 4. Chemical and Physical Information

- Again, my major issue is with the lack of citations. See the document for specific details.
- I'm not sure that the max/min pounds of cobalt on site is really that helpful…also, why is it expressed in pounds and not SI units???

***RESPONSE**:*

- Included citations in Chapter 4 as needed.

-EPA requires quantities to be reported to them in traditional units rather than SI units.

COMMENT: Chapter 5. Potential for Human Exposure

- Again, lots of narrative/text but where are the citations?
- Minor: just editing- superscripts and subscripts/consistency

***RESPONSE**:*

- Citations in summary have not been included but are listed in the text as needed.

-Accepted edits to superscripts and subscripts and edited others where needed.

COMMENT: Chapter 6. Adequacy of the Database

- No major issues- see document for specific details

***RESPONSE**: In text edits included in the profile.*

COMMENT: Chapter 7. Regulations and Guidelines

- No major issues.

***RESPONSE**: No response needed.*

Annotated Comments on the Profile- Reviewer 1

COMMENT: Citation ?

***RESPONSE**: This comment refers to the following sentence in section 1.1 (Overview and U.S. Exposures): "The largest use of metallic cobalt is in rechargeable batteries, followed by uses as super alloys in gas turbine aircraft engines." As per ATSDR's latest "Guidance for the Preparation of Toxicological Profiles" document, citations are not included in Chapter 1. No edits needed.*

COMMENT: Citation ?

***RESPONSE**: This comment refers to the following sentence in section 1.1 (Overview and U.S. Exposures): "These compounds are used as pigments in glass, ceramics, and paints; as catalysts in the petroleum industry; as paint driers and as trace element additives in agricultural soil-amendments and medicinal products." As per ATSDR's latest, "Guidance for the Preparation of Toxicological Profiles" document , citations are not included in Chapter 1. No edits needed.*

COMMENT: Where are the citations?

***RESPONSE**: This comment refers to the second paragraph in section 1.1 (Overview and U.S. Exposures). As per ATSDR's latest, "Guidance for the Preparation of Toxicological Profiles" document , citations are not included in Chapter 1. No edits needed.*

COMMENT: Citation ?

RESPONSE*: This comment refers to the following sentence in section 1.2 (Summary of Health Effects): "Cobalt ion in the body gives rise to inhibition of DNA repair, genotoxicity, and generation of reactive oxygen species (ROS) resulting in oxidative damage by cobalt." As per ATSDR's latest, "Guidance for the Preparation of Toxicological Profiles" document, citations are not included in Chapter 1. No edits needed.*

COMMENT: What about nephrological/kidney? Most metals have extensive literature on kidney toxicity.

RESPONSE*: This comment refers to the following sentence in section 1.2 (Summary of Health Effects): "Based on the current body of literature, the respiratory and hematological endpoints are the most evaluated in human toxicity studies and appear to be the most sensitive endpoints of cobalt toxicity." Based on the literature review conducted for cobalt, Renal effects were not identified as a sensitive endpoint after exposure to cobalt. However, Renal health effects are detailed in Chapter 2 Section 10. This profile is specific to cobalt and only health effects caused by cobalt exposure are included. No edits needed.*

COMMENT: Oral cobalt ingestion: please include Tvermoes et al. 2014 PMID: 24500148 (more recent publication regarding hematological parameters)

RESPONSE*: This comment refers to the Hematological Effects section in section 1.2 (Summary of Health Effects). The suggested citation was included and the following sentence was added: "Tvermoes et al. (2014) found no significant changes in hematological parameters following 90-day exposure to 1.0 mg/day of cobalt (0.08-0.19 mg/kg/day) in 10 volunteers."*

COMMENT: Define "chronic duration" here

RESPONSE*: This comment refers to the following sentence in section 1.3 (Minimal Risk Levels): "There were no studies that examined chronic-duration oral exposure to cobalt, and therefore the derivation of an oral chronic MRL was not possible." Since durations were defined at the start of section 1.2, no edits are needed here.*

COMMENT: In the inhalation table, I'm not sure if you can include intra tracheal instillation of nanoparticles. (PMID: 28923112).

RESPONSE*: This comment refers to Table 2-1 in section 2.1 (Introduction). Cobalt nanoparticles are detailed briefly Chapter 2 section 22 as per ATSDR's latest, "Guidance for the Preparation of Toxicological Profiles" document. This table focuses on inhalation exposure to cobalt metal and other inorganic forms of cobalt. No edits needed.*

COMMENT: Does intratracheal, intranasal instillation or oropharyngeal aspiration count? Or should it be mentioned in a separate section? There are several articles (Billing et al. 2020, Deng et al. 2021). I have no idea if it's accepatable for an ATSDR profile.

***RESPONSE**: This comment refers to the Inhalation section in section 2.2 (Death). Cobalt Nanoparticles are briefly discussed in Chapter 2 section 22. These routes of exposure were addressed in earlier responses to similar reviewer comments. These are not typically included in the inhalation category since these are not primary routes of exposure. This is in accordance with ATSDR's latest "Guidance for the Preparation of Toxicological Profiles" document.*

COMMENT: Results can also go under lung/respiratory section.

***RESPONSE**: This comment refers to the Inhalation section in section 2.11 (Dermal). Wahlqvist et al. 2020 assessed dermal effects but not respiratory effects of hard metal cobalt inhalation exposure. No edits needed.*

COMMENT: There is a case report of cobalt toxicity and visual impairment from a metallic hip prosthesis (Garcia et al. 2020). Also, Thakur et al. 2021 – CoCl2 on retinal cells (R28 cells).

***RESPONSE**: This comment refers to the following sentence in section 2.12 (Ocular): "There is a case report of cobalt toxicity and visual impairment from a metallic hip prosthesis (Garcia et al. 2020). Also, Thakur et al. 2021 – $CoCl_2$ on retinal cells (R28 cells)." Studies involving cobalt exposure from prosthetics are not included in accordance with ATSDR's latest "Guidance for the Preparation of Toxicological Profiles" document. Profile focuses on primary routes of exposure, inhalation, oral, and dermal. Thakur et al. 2021 study was published after the literature review for this profile was performed. No edits needed.*

COMMENT: Since there are no human studies with Co and carcinogenicity, as previously mentioned.

***RESPONSE**: This comment refers to the following sentences in 2.21 (Mechanism of Action): "Soluble and insoluble forms of cobalt give rise to toxicity and carcinogenicity following cellular uptake of the metal and subsequent release of cobalt ions its salts. These ions cause an immediate cascade of downstream biological effects. The extracellular release of cobalt ions from water-soluble compounds is transported into the cells thorough the ion channels or via endocytosis of poorly soluble cobalt compounds." The phrase "in animal models" was added and the sentence now reads: "Soluble and insoluble forms of cobalt give rise to toxicity and carcinogenicity in animal models following cellular uptake of the metal and subsequent release of cobalt ions from its salts. These ions elicit a cascade of downstream biological effects. The extracellular release of cobalt ions from water-soluble compounds is transported into the cells thorough the ion channels or via endocytosis of poorly soluble cobalt compounds."*

COMMENT: Citations here

RESPONSE*: This comment refers to the following sentence in section 2.22 (Cobalt Nanoparticles): "Primary target organs for CoNPs toxicity include the testicles, brain, and lungs." This is a summary statement for the text below, which contains citations. No edits needed.*

COMMENT: This applies to most if not all particles, which I would mention, rather than making it specific for Co (it's not).

RESPONSE*: This comment refers to the following sentence in section 3.1 (Toxicokinetics): "Absorption: Submicron size particles of cobalt can be almost completely absorbed through the respiratory tract, whereas larger particles may be moved after deposition in the respiratory tract by mucociliary clearance and swallowed." The text has been adjusted and the sentence now reads: "Absorption: Submicron size particles of a substance, such as cobalt, can be almost completely absorbed through the respiratory tract, whereas larger particles may be moved after deposition in the respiratory tract by mucociliary clearance and swallowed."*

COMMENT: James et al. 1994 is the same citation. Should only need to cite initially.

RESPONSE*: This comment refers to the following sentence in section 3.1.1 (Absorption): "Deposition of particulates greater than 2.5 µm occurs in the upper portion of the airway, whereas particulates less than 2.5 µm are deposited in the lower portion of the lungs." The repeated citation was deleted.*

COMMENT: Wahlquist et al. 2020 is addressed above as an inhalation study and reported associated dermal effects. If dermal absorption occurred, all relevant text should be reassessed and appropriately adjusted.

RESPONSE*: This comment refers to the following sentence in section 3.1.1 (Absorption): "Wahlquist et al. (2020) reported a statistically significant correlation between cobalt on the skin and uptake of cobalt in the blood in workers at hard metal production facilities, but not a relationship between cobalt on the skin and cobalt in urine." This sentence was deleted, as Wahlquist et al. 2020 is an inhalation exposure study.*

COMMENT: Please reassess this text if dermal exposure was not considered.

RESPONSE*: This comment refers to the following sentence in section 3.1.1 (Absorption): "The difference in skin exposure to urine correlation between the Wahlquist et al. (2020) study and Kettelarij et al. (2018) study may be in part due to the timing and number of sample collection." This sentence was deleted, as Wahlquist et al. 2020 is an inhalation exposure study.*

COMMENT: Be consistent – hr vs. h

RESPONSE*: This comment refers to the following sentence in section 3.1.1 (Absorption): "Using cobalt powder applied in human sweat, the reported steady state percutaneous permeation was 0.0123 ± 0.0054*

µg/cm2/hr. with a lag time of 1.55±0.71 hr, with much of the cobalt remaining in the skin." The "h" was changed to "hr" for consistency.

COMMENT: Also be consistent throughout using "cobalt" vs. abbreviated "Co"

***RESPONSE**: This comment refers to the following sentence in section 3.1.1 (Absorption): "Inaba and Suzuki-Yasumoto (1979) examined the absorption of 2.2x10-5 mg 60Co/kg as $CoCl_2$ in 1.4N HCl through 1 cm2 of intact or abraded skin of guinea pigs." 60Co is defined as cobalt-60 and the sentence now reads: "Inaba and Suzuki-Yasumoto (1979) examined the absorption of 2.2x10-5 mg cobalt -60 (60Co)/kg as $CoCl_2$ in 1.4N HCl through 1 cm2 of intact or abraded skin of guinea pigs."*

COMMENT: "golden hamsters" was previously capitalized – should it be lower case?

***RESPONSE**: This comment refers to the following sentence in section 3.1.2 (Distribution): "In Syrian golden hamsters, the carcass (23%) and the GI tract (60%) had the most cobalt 24 hours post-exposure to CoO (Wehner and Craig 1972). In swine, the kidney cortex and spleen had higher cobalt levels than controls (Kerfoot 1974). Since "golden hamsters" should be lower case, no edits are needed.*

COMMENT: Define these here

***RESPONSE**: This comment refers to the following sentence in section 3.3.2 (Biomarkers of Effect): FEV1 and FVC. These have been defined on first use and the acronyms are included in the glossary. No edits needed.*

COMMENT: Where are the citations?

***RESPONSE**: This comment refers to the following bullets in section 5.1 (Overview): "The general population may be exposed to cobalt through inhalation of ambient air and ingestion of food and drinking water (Davis and Fields 1958; Nemery et al. 1992). The general population may also be exposed to cobalt in consumer goods, like leather products and jewelry, and by using drilling and grinding tools that contain cobalt (Alinaghi et al. 2019; Bregnbak et al. 2017; Cheong et al. 2014; Sesana et al. 1994).*

Workers in the hard metal industry (tool production, grinding, etc.) and industries such as coal mining, metal mining, smelting, and refining, cobalt dye painters, and cobalt chemical production are exposed to higher levels of cobalt via airborne dust and direct contact (Afridi et al. 2009; Hewitt 1988; Kettelarij et al. 2018a; Linna et al. 2004; Raffin et al. 1988). Populations living near these industrial sites are also exposed to higher levels of cobalt (Cao et al. 2014; Cheyns et al. 2014; Han et al. 2020)."

This is a summary section. Citations are included in the relevant sections that follow. No edits needed.

COMMENT: I'm not sure the rationale behind including minimum and maximum amount on site or if it actually adds much to the document?

RESPONSE*: This comment refers to Table 5-1 in section 5.2.1 (Production). This table and the information within are required by ATSDR and outlined in ATSDR's latest "Guidance for the Preparation of Toxicological Profiles". These are standard data reported as required by EPA. No edits needed.*

COMMENT: Or define FEV1 etc here??

RESPONSE*: The terms are defined in Chapter 2 where it is first used and in Appendix G. Acronyms Abbreviations, and Symbols.*

Comments provided by Peer Reviewer #2

ATSDR Charge Questions and Responses

Chapter 1. Relevance to Public Health

QUESTION: Do you agree with those effects known to occur in humans as reported in the text? If not, please explain why and provide a copy of additional references you would cite and indicate where (in the text) these references should be included.

COMMENT: Yes, I agree: it is adequatelty reported that non-cancer lung effects are observed in humans (following inhalation), that hematological effects may be observed in human following oral exposure, and that skin sensitization may occur in humans following dermal exposure to cobalt substances.

RESPONSE: *No response needed.*

QUESTION: Are the effects only observed in animals likely to be of concern to humans? Why or why not? If you do not agree, please explain.

COMMENT: I agree with the way the animal findings, lung-cancer following inhalation exposure, are presented, and that these have not been observed in humans.

RESPONSE: *No response needed.*

QUESTION: Have exposure conditions been adequately described? If you disagree, please explain

COMMENT: I agree that exposures have been adequately described, and that there has been an adequate differentiation between the types of effects caused by the different types of exposure.

RESPONSE: *No response needed.*

Minimum Risk Levels (MRLs)

QUESTION: If no MRLs have been derived, do you agree that the data do not support such a derivation? Please explain.

COMMENT: I agree with the occasisons where no MRL was derived, based on isufficient data (e.g. for short term inhalation effects).

RESPONSE: *No response needed.*

QUESTION: If MRLs have been derived, do you agree with the proposed MRL values? Explain. If you disagree, please specify the MRL value that you would propose.

COMMENT: *No response provided.*

RESPONSE: *Response provided for each question below.*

QUESTION (Subset of preceding question): Do you agree/disagree with each component of the total uncertainty factor? Explain. If you disagree, please specify the uncertainty factor(s) that you propose.

COMMENT: MRL Inhalation Chronic.

I disagree with several points of the calculation of the MRL.

A – selection of key study: the study selected as key study (Nemery et al, 1992) has several weaknesses, e.g. it is a cross-sectional study design with no pre- or post observation follow up. The co-exposures are poorly identified and of unknown nature. This is a concern, since the diamond polishing "industry" in Belgium was a set of small-scale workshops in Antwerp, where individual workers used unknown and "secret" techniques to improve or elongate the work life of their polishing disks (sometimes with glues). Interestingly, the elevated respiratory toxicity was observed in 5 of the 10 workshops. The 5 workshops with elevated findings also had – on the whole- elevated cobalt concentrations in the air, but there was no correlation between symptoms and cobalt exposure on an individual level. This is stated in the paper (correlation only on the "group level"; individual data are not shown). Also, the type of effect observed is not exactly matching the obstructive effects (reduction in FEV1/FVC ratio), but resembles more a pneumoconiosis type effect (restrictive). Therefore, several aspects required to have confidence in the data are lacking: no long-term observation, no dose response (on an individual scale), effect not 100% matching the known cobalt effect.

There are better studies to derive a chronic MRL for inhalation. Probably the best cohort is the one described by Sauni et al of 2010 (endpoint asthma), or the cancer study of 2017.

Exposures and co-exposures are well defined on this site. While the 2010 study design, a case series, is also not usually used for MRL derivation, there are useful observations in this study: thre was a long-term follow up of symptoms and -more interestingly- an observation of a lack of asthma cases/symptoms during the observation period in the Chemicals department, where there were no co-exposures to irritant gases. The highest exposures in this department (with confirmed lack of co-exposures) can be taken as human NOAEL for the reduction in FEV1/FVC ratio that is observed in the other departments.

The MRL, in my understanding, corresponds to the DNEL for the general population (an exposure level at which no adverse health outcome is expected at chronic exposures). The DNEL calculation for the general population based on Sauni et al 2010 is attached. The relevant section is 4.3, where the MRL equivalent (chronic DNEL inhalation for consumers and humans via environment) is 0.008 mg Co/m³.

For oral exposure, I propose to use our sub-chronic, guideline compliant rat study (90-day exposure), OECD 408 with reproductive toxicity screening as key study. Guideline complaint studies are more easily "converted" into human corresponding risk estimates, as they follow standard study durations that can be converted by agreed AFs. The OECD 408 study also is for a longer duration and at lower exposures than the study by Awoyemi et al 2017, and hematological effects were observed by us with a dose response. The DNEL (general population, chronic duration) based on this study is also attached as my alternative proposal to the MRL as in the draft cobalt ATSDR. It is in section 3.4 of the respective document and is at just below 0.03 mg/kg bw/day.

My comment on not needing the full AF of 10 for chemicals that undergo no metabolisation is reflected in the AFs chosen in the attached documents, that is for inter-species variability, the AF for correction for differences in metabolic rate (AS) can be set at 1. AF for the remaining differences (e.g. toxicokinetics/-dynamics) is set at 2.5.

(This reduction of AF is only relevant for the oral route. I may have incorrectly made this comment in an inhalation section in the draft ATSRD document. I apologize for this error and ask the receiver of the comments to ignore the "reduced AF for metabolic rate" in the context of inhalation).

RESPONSE: ***MRL for chronic-duration inhalation exposure****: ATSDR is retaining the MRL for chronic inhalation based on Nemery et al . (1992).*

Sauni et al. 2017 titled "Cancer incidence among Finnish male cobalt production workers in 1969-2013: a cohort study" cannot be used to derive an MRL as this study examines cancer incidence among Finnish male cobalt production workers. ATSDR does not use cancer as a health effect to base an MRL on, this would rule out Sauni et al. 2017.

Sauni et al. 2010 identified 21 cases of asthma after exposure to cobalt where the workers were also exposed to SO_2 and ammonia until 1987. After that, due to regulatory changes, there was cessation of use of the irritant gases, which decreased the case of asthma to 1. Therefore, in Sauni et al. 2010, it is likely that the health effects are being driven by exposure to SO_2 and ammonia and not by cobalt alone. SO_2 is a known respiratory irritant supported by numerous studies (Hubert and Loving, 1991, Anderson et al. 2006; ATSDR 1998, Toxicological Profile for Sulfur Dioxide). The discussion pertaining to Sauni et al. (2010) will be included in the MRL worksheet.

The following text is included in the ToxProfile and MRL worksheet "Sauni et al. (2010) conducted a case study of occupational asthma in cobalt plant workers in Finland from 1967 -2003 where the mean air concentrations of cobalt in different departments ranged from 0.03 to 0.15 mg/m3. Until 1987, cobalt was being produced from pyrite ore concentrate which led to co-exposures with irritant gases including sulfur dioxide (SO2) and ammonia (NH3) that are known respiratory irritants (Andersson et al. 2006; ATSDR 1998; Huber and Loving 1991). After 1987, cobalt was produced using by-products of metallurgic industry as raw material which eliminated the co-exposure to the irritant gases and the incidence of asthma decreased to only 1 case between 1987-2003 compared to 21 cases between 1967-1987(Sauni et al. 2010). Therefore, it is likely that the health effects observed in this study were due to the co-exposure to sulphur dioxide and ammonia and not cobalt alone. For this reason, Sauni et al. (2010) cannot be used to derive an MRL."

MRL for intermediate-duration oral exposure*: ATSDR is retaining the MRL derived from Davis and Fields 1958. The derivation of DNEL by The Cobalt REACH Consortium is based on the sub-chronic, guideline compliant rat study (90-day exposure), OECD 408 with reproductive toxicity screening which was peer-reviewed and published as Danzeisen et al. (2020). The DNEL derived value is effectively identical to our intermediate-duration oral MRL (0.03 mg/k/d for the MRL and 0.0298 mg/kg/d DNEL which can be rounded to 0.03 mg/k/d). The UFs used to derive the DNEL were a total UF of 25 which included a UF of 5 for human variability and the NOAEL in mg/kg/day was converted to µg/kg/day. Using the equation DNEL = NOAEL/Overall UF, the calculated value for DNEL was = 3000 ug/25=120 ug/k/d or equivalent of cobalt of 29.8 ug/k/d or 0.0298 mg/kg/d. Since both values of DNEL and MRL converge on very similar numbers, ATSDR will be retaining the MRL derived using the human exposure study by Davis and Fields 1958. The doses used to derive the DNEL as indicated in Danzeisen et el. (2020) lend strong support to the ATSDR derived MRL. This discussion will be included in the MRL worksheet.*

The following text is included in the ToxProfile, APPENDIX A. ATSDR MINIMAL RISK LEVELS AND WORKSHEETS "Danzeisen et al. (2020) was used to derive a Derived No-Effect Level (DNEL) for oral cobalt exposure which was calculated as 0.0298 mg Co/kg/day by the Cobalt REACH Consortium. The UFs used to derive the DNEL were a total UF of 25 which included UF of 5 for human variability, and

the NOAEL in mg/kg/day was converted to µg/kg/day. The calculated DNEL was 29.8 µg Co/kg/day or 0.0298 mg Co/kg/day which can be rounded to 0.03 mg Co/kg/day. The derived DNEL is effectively identical to ATSDR's intermediate-duration oral MRL (0.03 mg Co/kg/day). Because both values of DNEL and MRL converge on very similar numbers, ATSDR will be retaining the intermediate- duration oral MRL derived from the human exposure study by Davis and Fields 1958. The doses used to derive the DNEL as indicated in Danzeisen et el. (2020) lend strong support to the derived MRL."

The UFs used to derive an ATSDR MRL are based on ATSDR guidelines stated in the ATSDR guidelines "Guidance for the Preparation of Toxicological Profiles".

QUESTION (Subset of preceding question): Please comment on any aspect of our MRL database assessment that you feel should be addressed.

COMMENT: *No response provided.*

RESPONSE: *No response needed.*

Chapter 2. Health Effects

QUESTION: Do the health effect conclusions made in Chapter 2 adequately reflect the findings in the published literature? If not, please suggest appropriate changes.

COMMENT: Overall, I agree. One exception is genotoxicity/mutagenicity, where the inclusion of a key publication (in my view), and the conclusions therein, is recommended. See citation below. Please note that the paper is incorrectly labelled as a "review" – it does in fact contain original data**.**

Review > Regul Toxicol Pharmacol. 2015 Oct;73(1):311-38. doi: 10.1016/j.yrtph.2015.07.016. Epub 2015 Jul 22.

New investigations into the genotoxicity of cobalt compounds and their impact on overall assessment of genotoxic risk

David Kirkland [1], Tom Brock [2], Hasnaà Haddouk [3], Victoria Hargeaves [4], Melvyn Lloyd [4], Sarah Mc Garry [4], Raymond Proudlock [5], Séverine Sarlang [3], Katherina Sewald [6], Guillaume Sire [3], Andrea Sokolowski [7], Christina Ziemann [6]

RESPONSE: *Kirkland et al. (2015) was reviewed and pertinent information was included in Chapter 2, section 30- Genotoxicity. The genotoxic effects of exposure to inorganic cobalt compounds have been include in Table 2-7 Genotoxicity of Cobalt In Vivo and Table 2 8. Genotoxicity of Cobalt In Vitro. The following text has been included in the Chapter 2, Section 30 "Oral exposure to cobalt compounds studied by Kirkland et al. (2015) did not elicit any chromosomal aberrations in the bone marrow or sperm."*

QUESTION: Were adequately designed human studies identified in the text (i.e., good exposure data, sufficiently long period of exposure to account for observed health effects, adequate control for confounding factors)? Were the major study limitations sufficiently described in the text without going into lengthy discussions? If study limitations were not adequately addressed, please suggest appropriate changes.

COMMENT: I was missing the cancer cohorts by Marsh et al and Sauni et al, both 2017. Sauni 2017 is cited above. Below, please find Marsh et al, all 5 country cohorts and pooled study. The pooled study of all individual country cohorts (#8 of list) is probably the most suitable to gain an overview over inhalation effects from hard metal exposure (cobalt concentrations in air and in some cases in urine were measured or estimated).

1 Mortality Among Hardmetal Production Workers: German Historical Cohort Study.
Morfeld P, Groß JV, Erren TC, Noll B, Yong M, Kennedy KJ, Esmen NA, Zimmerman SD, Buchanich JM, Marsh GM.
J Occup Environ Med. 2017 Dec;59(12):e288-e296. doi: 10.1097/JOM.0000000000001061.
PMID: 29215484

2 Mortality Among Hardmetal Production Workers: Swedish Measurement Data and Exposure Assessment.
Westberg H, Bryngelsson IL, Marsh G, Kennedy K, Buchanich J, Zimmerman S, Esmen N, Svartengren M.
J Occup Environ Med. 2017 Dec;59(12):e327-e341. doi: 10.1097/JOM.0000000000001147.
PMID: 29215486

3 Mortality Among Hardmetal Production Workers: The Swedish Cohort.
Westberg H, Bryngelsson IL, Marsh G, Buchanich J, Zimmerman S, Kennedy K, Esmen N, Svartengren M.
J Occup Environ Med. 2017 Dec;59(12):e263-e274. doi: 10.1097/JOM.0000000000001054.
PMID: 29215483

4 Mortality Among Hardmetal Production Workers: Occupational Exposures.
Kennedy KJ, Esmen NA, Buchanich JM, Zimmerman S, Sleeuwenhoek AJ, Marsh GM.
J Occup Environ Med. 2017 Dec;59(12):e297-e305. doi: 10.1097/JOM.0000000000001068.
PMID: 28704227

5 Cite Share
Mortality Among Hardmetal Production Workers: US Cohort and Nested Case-Control Studies.
Marsh GM, Buchanich JM, Zimmerman S, Liu Y, Balmert LC, Esmen NA, Kennedy KJ.
J Occup Environ Med. 2017 Dec;59(12):e306-e326. doi: 10.1097/JOM.0000000000001075.
PMID: 29215485

6 Cite Share
Cancer Incidence Among Hardmetal Production Workers: The Swedish Cohort.
Svartengren M, Bryngelsson IL, Marsh G, Buchanich J, Zimmerman S, Kennedy K, Esmen N, Westberg H.
J Occup Environ Med. 2017 Dec;59(12):e365-e373. doi: 10.1097/JOM.0000000000001185.
PMID: 29215488 Free PMC article.

7 Cite Share
Mortality Among Hardmetal Production Workers: UK Cohort and Nested Case-Control Studies.
McElvenny DM, MacCalman LA, Sleeuwenhoek A, Davis A, Miller BG, Alexander C, Cowie H, Cherrie JW, Kennedy KJ, Esmen NA, Zimmerman SD, Buchanich JM, Marsh GM.
J Occup Environ Med. 2017 Dec;59(12):e275-e281. doi: 10.1097/JOM.0000000000001036.
PMID: 28697060

8 Cite Share
Mortality Among Hardmetal Production Workers: Pooled Analysis of Cohort Data From an International Investigation.
Marsh GM, Buchanich JM, Zimmerman S, Liu Y, Balmert LC, Graves J, Kennedy KJ, Esmen NA, Moshammer H, Morfeld P, Erren T, Groß JV, Yong M, Svartengren M, Westberg H, McElvenny D, Cherrie JW.
J Occup Environ Med. 2017 Dec;59(12):e342-e364. doi: 10.1097/JOM.0000000000001151.
PMID: 29215487

9 Cite Share
Mortality Among Hardmetal Production Workers: A Retrospective Cohort Study in the Austrian Hardmetal Industry.
Wallner P, Kundi M, Moshammer H, Zimmerman SD, Buchanich JM, Marsh GM.
J Occup Environ Med. 2017 Dec;59(12):e282-e287. doi: 10.1097/JOM.0000000000001046.
PMID: 28665836

RESPONSE: *The studies suggested by Reviewer #2 have been reviewed and all studies examined cancer effects and are included in Chapter 2, section 19- Cancer. The following text was added in the section*

"Exposure to cobalt, tungsten, and nickel and cancer mortality risk was evaluated in an international cohort of hard metal production workers (Marsh et al. 2017b). Workers from 3 companies, 17 sites among 5 countries, including the United States, Austria, Germany, Sweden, and the United Kingdom were evaluated. Information on deaths was obtained from various national datasets, and phone interviews were completed for participants when possible. These interviews provided information on demographic and lifestyle factors. Kennedy et al. (2017) described the job class plus exposure matrix that

was used and reported the estimated cobalt, nickel, and tungsten exposures. Employee history was obtained from occupational records. Among the US cohort which included eight sites, there was no increased lung cancer mortality risk or trends in SMRs from long term exposure to cobalt or from the other metals studied (Marsh et al. 2017a). Standardized mortality ratios were not statistically higher by sex and while two plants observed excess lung cancer mortality, this was not statistically significant (Marsh et al. 2017a). Study authors state that the lung cancer risks were higher in females than in males in Germany, the US, and Sweden likely due to lifestyle and behavioral factors, such as increased smoking and not from occupational exposure (Marsh et al. 2017a). When pooling data from all international cohorts, there was a slight excess in all cancer and lung cancer mortality; however, there was no evidence of an exposure-response relationship for lung cancer (Marsh et al. 2017b). Additionally, there was no indication that occupation duration nor cumulative exposure to cobalt impacted lung cancer mortality risk. In other studies conducted at hard metal production factories in the United Kingdom and Europe, the study authors found no significant exposure-response relationship between cancer and inhalation exposure to cobalt (McElvenny et al. 2017; Morfeld et al. 2017; Sauni et al. 2017; Wallner et al. 2017; Westberg et al. 2017a; Westberg et al. 2017b)."

QUESTION: Were adequately designed animal studies identified in the text (i.e., adequate number of animals, good animal care, accounting for competing causes of death, sufficient number of dose groups, and sufficient magnitude of dose levels)? If not, does the inadequate design negate the utility of the study? Please explain.

COMMENT: Generally, I felt that this was adequately described, e.g., in some cases pointing to the very high doses that may have resulted in secondary effects.

RESPONSE: *No response needed.*

QUESTION: Were the animal species appropriate for the most significant toxicological endpoint of the study? If not, which animal species would be more appropriate and why?

COMMENT: OK from my viewpoint.

RESPONSE: *No response needed.*

QUESTION: Has adequate attention been paid to dose-response relationships for both human and animal data? Please explain.

COMMENT: See my comment above, there was a lack of DR in Nemery that was not acknowledged. In general, there are not that many studies with a good DR in the public domain for cobalt, so overall this was appropriately reflected.

RESPONSE: *No response needed.*

QUESTION: Are you aware of any studies that are not included in the profile that may be important in evaluating the toxicity of the substance? Please provide a copy of each study and indicate where in the text each study should be included.

COMMENT: See above studies for cancer and genotoxicity.

RESPONSE: *Studies suggested by the reviewer in previous comments have been discussed in previous responses and included in the appropriate sections in the profile as described in previous responses.*

QUESTION: Are you aware of any studies that are not included in the profile that may be relevant to deriving MRLs for any of the substance isomers? Please provide a copy if this is a new reference.

COMMENT: Not sure this is relevant – there are no isomers of cobalt.

RESPONSE: *No response needed.*

QUESTION: Were all appropriate NOAELs and/or LOAELs identified for each study (both in the text and the Levels of Significant Exposure (LSE) tables and figures)? If not, did the text provide adequate justification for excluding NOAELs/LOAELs including, but not limited to, citing study limitations? Please suggest appropriate changes.

COMMENT: These seemed OK, as far as I can see**.**

RESPONSE: *No response needed.*

QUESTION: Do you agree with the categorization of "less serious" or "serious" for the effects cited in the LSE tables? If not, please explain why and suggest appropriate changes.

COMMENT: Agree.

RESPONSE: *No response needed.*

QUESTION: Have all possible mechanisms of action been discussed within their relevant health effect section? If not, please explain. If citing a new reference, please provide a copy and indicate where (in the text) it should be included.

COMMENT: I believe all relevant mechanisms are discussed and included.

RESPONSE: *No response needed.*

QUESTION: Are the conclusions appropriate given the overall database? If not, please discuss your own conclusions based on the data provided and other data provided to you but not presented in the text.

COMMENT: I agree with the general conclusions on hazard. My only diverging view is on selection of key studies for risk values, see above.

RESPONSE: *No response needed.*

QUESTION: RADIOACTIVE COBALT STUDIES: Are you aware of any studies using radioactive cobalt isotopes that would improve the information presented in this chapter.

COMMENT: No.

RESPONSE: *No response needed.*

QUESTION: NANOPARTICLES: Is the section regarding cobalt nanoparticles appropriately detailed and accurate? If not, please identify its shortcomings, recommend topics to include, identify where those topics should be addressed in the text, and provide copies of the new references supporting those topics.

COMMENT: I believe that inclusion of the nanoparticle topic would probably "explode" this document into an unmanageable scale. I agree with the current level of coverage of the nano topic.

RESPONSE: *No response needed.*

Chapter 3. Toxicokinetics, Susceptible Populations, Biomarkers, Chemical Interactions

QUESTION: Is there adequate discussion of absorption, distribution, metabolism, and excretion of the substance? If not, suggest ways to improve the text.

COMMENT: Answer to all questions: I believe that these aspects have been appropriately covered. Small comments, often editorial, are in the text.

RESPONSE: *Editorial corrections have been made in text within the profile*.

QUESTION: Have all available pharmacokinetic/pharmacodynamic models and supporting data been presented? If not, please explain.

COMMENT: Answer to all questions: I believe that these aspects have been appropriately covered. Small comments, often editorial, are in the text.

RESPONSE: *Editorial corrections have been made in text within the profile.*

QUESTION: Is there adequate discussion of the differences in toxicokinetics between humans and animals? Is there adequate discussion of the relevance of animal toxicokinetic information for humans?

COMMENT: Answer to all questions: I believe that these aspects have been appropriately covered. Small comments, often editorial, are in the text.

RESPONSE: *Editorial corrections have been made in text within the profile.*

QUESTION: Are there any data relevant to child health and developmental effects that have not been discussed in the profile and should be? Please provide any relevant references.

COMMENT: Answer to all questions: I believe that these aspects have been appropriately covered. Small comments, often editorial, are in the text.

RESPONSE: *Editorial corrections have been made in text within the profile.*

QUESTION: Is there a discussion of populations at higher risk of susceptibility? Do you agree with the choice of populations? Please explain and provide any additional relevant references.

COMMENT: Answer to all questions: I believe that these aspects have been appropriately covered. Small comments, often editorial, are in the text.

RESPONSE: *Editorial corrections have been made in text within the profile.*

QUESTION: Are the biomarkers of exposure specific for the substance? Please explain.

COMMENT: Answer to all questions: I believe that these aspects have been appropriately covered. Small comments, often editorial, are in the text.

RESPONSE: *Editorial corrections have been made in text within the profile.*

QUESTION: Are the biomarkers of effect specific for the substance? Please explain.

COMMENT: Answer to all questions: I believe that these aspects have been appropriately covered. Small comments, often editorial, are in the text.

RESPONSE: *Editorial corrections have been made in text within the profile.*

QUESTION: Is there adequate discussion of the interactive effects with other substances? Does the discussion concentrate on those effects that might occur at hazardous waste sites? Please explain and provide any additional references.

COMMENT: Answer to all questions: I believe that these aspects have been appropriately covered. Small comments, often editorial, are in the text.

RESPONSE: *Editorial corrections have been made in text within the profile.*

QUESTION: If interactive effects with other substances are known, does the text discuss the mechanisms of these interactions? Please explain and provide any additional references.

COMMENT: Answer to all questions: I believe that these aspects have been appropriately covered. Small comments, often editorial, are in the text.

RESPONSE: *Editorial corrections have been made in text within the profile.*

Chapter 4. Chemical and Physical Information

QUESTION: Are any of the values or information provided in the chemical and physical properties tables wrong or missing? Please explain and provide any additional references.

COMMENT: The values appear to be correct.

RESPONSE: *No response needed.*

QUESTION: Is information provided on the various forms of the substance? Please explain.

COMMENT: The values appear to be correct.

RESPONSE: *No response needed.*

Chapter 5. Potential for Human Exposure

QUESTION: Is the information on production, import/export, use, and disposal of the substance complete? Please explain and provide any additional relevant references.

COMMENT: I have no data relating to these topics, and cannot comment on their completeness or correctness.

RESPONSE: *No response needed.*

QUESTION: Has the text appropriately traced the substance from its point of release to the environment until it reaches the receptor population? Does the text provide sufficient and technically sound information regarding the extent of occurrence at NPL sites? Do you know of other relevant information? Please provide references for added information.

COMMENT: Questions 2 – 5: this is not my area of expertise, and I cannot comment. However, the sources, pathways, exposures description seemed reasonable.

RESPONSE: *No response needed.*

QUESTION: Does the text cover pertinent information relative to transport, partitioning, transformation, and degradation of the substance in all media? Do you know of other relevant information? Please provide references for added information.

COMMENT: Questions 2 – 5: this is not my area of expertise, and I cannot comment. However, the sources, pathways, exposures description seemed reasonable.

RESPONSE: *No response needed.*

QUESTION: Does the text provide information on levels monitored or estimated in the environment, including background levels? Are proper units used for each medium? Does the information include the form of the substance measured? Is there an adequate discussion of the quality of the information? Do you know of other relevant information? Please provide references for added information.

COMMENT: Questions 2 – 5: this is not my area of expertise, and I cannot comment. However, the sources, pathways, exposures description seemed reasonable.

RESPONSE: *No response needed.*

QUESTION: Does the text describe sources and pathways of exposure for the general population and occupations involved in the handling of the substance, as well as populations with potentially high exposures? Do you agree with the selection of these populations? If not, why? Which additional populations should be included in this section?

COMMENT: Questions 2 – 5: this is not my area of expertise, and I cannot comment. However, the sources, pathways, exposures description seemed reasonable.

RESPONSE: *No response needed.*

Chapter 6. Adequacy of the Database

QUESTION: Do you know of other studies that may fill a data gap? Please provide any relevant references.

COMMENT: Question 1 – 3: no further studies to my knowledge that could fill any of the data gaps. I agree with the data gaps identified, e.g. chronic oral in mammals. Data are presented in neutral and fair way.

RESPONSE: *No response needed.*

QUESTION: Do you agree with the identified data needs? Please explain.

COMMENT: Question 1 – 3: no further studies to my knowledge that could fill any of the data gaps. I agree with the data gaps identified, e.g. chronic oral in mammals. Data are presented in neutral and fair way.

RESPONSE: *No response needed.*

QUESTION: Are the data needs presented in a neutral, non-judgmental fashion? Please note any bias in the text.

COMMENT: Question 1 – 3: no further studies to my knowledge that could fill any of the data gaps. I agree with the data gaps identified, e.g. chronic oral in mammals. Data are presented in neutral and fair way**.**

RESPONSE: *No response needed.*

Chapter 7. Regulations and Guidelines

QUESTION: Are you aware of any additional regulations or guidelines that should be included? Please provide citations.

COMMENT: Not aware of anything to add or remove.

RESPONSE: *No response needed.*

QUESTION: Are there any that should be removed? Please explain.

COMMENT: Not aware of anything to add or remove.

RESPONSE: *No response needed.*

Additional References from Reviewer*

**These are references cited within the reviewer's individual comments. Responses to the reviewer's comments specify the disposition of these references within the toxicological profile.*

Appendices

QUESTION: Please provide any comments on the content, presentation, etc. of the included appendices.

COMMENT: *No response provided.*

RESPONSE: *No response needed.*

Annotated Comments on the Profile

COMMENT: And rumen animal feed

RESPONSE*: This comment refers to the following sentence in section 1.1 (Overview and U.S. Exposures): "These compounds are used as pigments in glass, ceramics, and paints; as catalysts in the petroleum industry; as paint driers and as trace element additives in agricultural soil-amendments and medicinal products." The suggested edit has been included and the sentence now reads: "These compounds are used as pigments, in glass, ceramics, and paints; as catalysts in the petroleum and other industries, as paint driers, animal feed additives, and are a part of Vitamin B_{12} (USGS 2019); they are also used as trace element additives in agricultural soil-amendments (Biofeed 2021) and medicinal products (Chang et al. 2010)."*

COMMENT: Cardiac function was affected in the cohort of beer-drinkers in Quebec (see the original studies by Alexander, 1972), however, not in occupationally exposed individuals, see the study by Lantin 2013 in OEM.

RESPONSE*: This comment refers to the following sentence in section 1.2 (Summary of Health Effects): "Cobalt inhalation also affects cardiac function and causes allergic dermatitis manifesting as eczema and erythema." This portion is discussing cardiac effects of cobalt inhalation, so no edits are needed. Cardiac health effects associated with oral exposure to cobalt are discussed in detail in Chapter 2 Section 5 Cardiovascular.*

COMMENT: Bottom box Figure 1-1. Exposure concentrations are cobalt in presence of occupational co-exposures to e.g. diamond dust or irritant gases, is this assumption correct? To my knowledge, cobalt in the absence of co-exposures has a NOAEC of 0.12 mg Co/m3 (Sauni, 2010), study on occupational asthma.

RESPONSE*: This comment refers to Figure 1-1 in section 1.2 (Summary of Health Effects). Sauni et al. 2010 indicates 21 cases of asthma after exposure to cobalt where the workers were also exposed to irritant gases of SO2 and ammonia. After cessation of use of these irritant gases at the workplace, the number of asthma cases decreased to 1. Therefore, in Sauni et al. 2010, it is likely that the health effects were due to exposure to these irritant gases. No edits needed.*

COMMENT: Typogrph.error in 3rd box from top: infraction should be infarction

RESPONSE*: This comment refers to Figure 1-1 in section 1.2 (Summary of Health Effects). The figure was updated to fix the spelling in the third box from the top.*

COMMENT: Is lack of metabolization of Co (ion) considered in UFs? The UF for intra- or inter-species differences if formation of metabolites is not required for inorganics, as these are not further metabolized.

RESPONSE*: This comment refers to Table 1-1 in section 1.3 (Minimal Risk Levels). The studies used to derive MRLs presented in Table1-1 examine the effects of exposure to inorganic cobalt compounds. There are no additional uncertainty factors used here as Co is an inorganic substance. There are no additional uncertainty factors used here as Co is an inorganic substance. The UF plus MF of 30 is to account for human variability (UF of 10) and prolonged exposure that might result in greater and potentially permanent harm (MF of 3).Since this study was conducted in humans with small n, the UF considered to derive an MRL includes human variability only. No intra- or inter-species differences factors are considered as the study is in humans.*

COMMENT: In case also "no effect" studies are included in this analysis, then it is unclear why the endpoint cancer only lists animal studies. There are several published cancer cohorts in cobalt exposed workers, e.g. Marsh et al (2017), Sauni et al (2017) and previous studies by Mur/Moulin.

RESPONSE*: This comment refers to Figure 2-1 in section 2.1 (Introduction). The figure was updated to include human cancer studies in the study counts.*

COMMENT: Does the asterisk refer to the heading? If yes, please include "*" .0in above heading (Fig 2-1)

RESPONSE*: This comment refers to Figure 2-1 in section 2.1 (Introduction). The suggested edit was included and an asterisk was added below the heading.*

COMMENT: Redundant, delete on of the two words

RESPONSE*: This comment refers to the following sentence in section 2.1 (Introduction): "Chronic animal exposure caused inflammation in the nose, larynx, and lung along combined with emphysema and lesions in the respiratory tract." The suggested edit was included and the sentence now reads: "Chronic-duration animal exposure caused inflammation in the nose, larynx, and lung combined with emphysema and lesions in the respiratory tract."*

COMMENT: Pls spell out.

RESPONSE*: This comment refers to the following sentence in section 2.1 (Introduction): "In the study by Lantin et al. (2011), IEI was significantly (P< 0.001) correlated with mean corpuscular hemoglobin concentration (MCHC) in both univariate and multivariate regression analyses but there was no significant relationship between the IEI and the red cell count (polycythemia) even after occupational exposure to inhaled cobalt." The acronym was spelled out and the sentence now reads: "In the study by Lantin et al. (2011), the integrated exposure index (IEI) was significantly (P< 0.001) correlated with mean corpuscular hemoglobin concentration (MCHC) in both univariate and multivariate regression analyses, but there was no significant relationship between the IEI and the red cell count (red cell count not affected), even after occupational exposure to inhaled cobalt." The term polycythemia has been defined in the profile at the start of Chapter 1 and 2 as "When addressed in this profile, polycythemia refers to absolute polycythemia, which is an increase in red cell mass from exposure to a substance, such as cobalt. This profile does not address other forms or causes of polycythemia." Additional text has been included in the profile to indicate how the study authors have defined the term in each study where the term polycythemia has been mentioned.*

COMMENT: I understand that the acronyms are at the end of the table…. Consider clarifying these at the top of the table, as it is difficult to scroll there and back…. (table is very long)

RESPONSE*: This comment refers to Table 2-1 in section 2.1 (Introduction). This table has been developed in accordance with ATSDR guidelines as detailed in "Guidance for the Preparation of Toxicological Profiles". No edits needed.*

COMMENT: Is something like /m3 missing?

RESPONSE*: This comment refers to Table 2-4 in section 2.1 (Introduction). This study presents exposure as mg-years. No edits needed.*

COMMENT: Suggestion to include the hard metal cohorts by Marsh et al (2017): cobalt measurements were as mg Co/m3 in workplace atmosphere or urinary cobalt. Co-exposures are well documented and occurred only to hard metal (W and C).

Kennedy KJ, Esmen NA, Buchanich JM, Zimmerman S, Sleeuwenhoek AJ, Marsh GM. 2017. Mortality among hardmetal production workers: Occupational exposures. J Occup Environ Med. 59(12):e297-e305.

Marsh GM, Buchanich JM, Zimmerman S, Liu Y, Balmert LC, Esmen NA, Kennedy KJ. 2017a. Mortality among hardmetal production workers: US cohort and nested case-control studies. J Occup Environ Med. 59(12):e306-e326.

Marsh GM, Buchanich JM, Zimmerman S, Liu Y, Balmert LC, Graves J, Kennedy KJ, Esmen NA, Moshammer H, Morfeld P et al. 2017b. Mortality among hardmetal production workers: Pooled analysis of cohort data from an international investigation. J Occup Environ Med. 59(12):e342-e364.

McElvenny DM, MacCalman LA, Sleeuwenhoek A, Davis A, Miller BG, Alexander C, Cowie H, Cherrie JW, Kennedy KJ, Esmen NA et al. 2017. Mortality among hardmetal production workers: Uk cohort and nested case-control studies. J Occup Environ Med. 59(12):e275-e281.

Morfeld P, Gross JV, Erren TC, Noll B, Yong M, Kennedy KJ, Esmen NA, Zimmerman SD, Buchanich JM, Marsh GM. 2017. Mortality among hardmetal production workers: German historical cohort study. J Occup Environ Med. 59(12):e288-e296.

Wallner P, Kundi M, Moshammer H, Zimmerman SD, Buchanich JM, Marsh GM. 2017. Mortality among hardmetal production workers: A retrospective cohort study in the austrian hardmetal industry. J Occup Environ Med. 59(12):e282-e287.

Wehner AP, Busch RH, Olson RJ, Craig DK. 1977. Chronic inhalation of cobalt oxide and cigarette smoke by hamsters. Am Ind Hyg Assoc J. 38(7):338-346.

Westberg H, Bryngelsson IL, Marsh G, Buchanich J, Zimmerman S, Kennedy K, Esmen N, Svartengren M. 2017a. Mortality among hardmetal production workers: The swedish cohort. J Occup Environ Med. 59(12):e263-e274.

Westberg H, Bryngelsson IL, Marsh G, Kennedy K, Buchanich J, Zimmerman S, Esmen N, Svartengren M. 2017b. Mortality among hardmetal production workers: Swedish measurement data and exposure assessment. J Occup Environ Med. 59(12):e327-e341.

Wallner P, Kundi M, Moshammer H, Zimmerman SD, Buchanich JM, Marsh GM. 2017. Mortality among hardmetal production workers: A retrospective cohort study in the austrian hardmetal industry. J Occup Environ Med. 59(12):e282-e287.

Westberg H, Bryngelsson IL, Marsh G, Buchanich J, Zimmerman S, Kennedy K, Esmen N, Svartengren M. 2017a. Mortality among hardmetal production workers: The swedish cohort. J Occup Environ Med. 59(12):e263-e274.

Westberg H, Bryngelsson IL, Marsh G, Kennedy K, Buchanich J, Zimmerman S, Esmen N, Svartengren M. 2017b. Mortality among hardmetal production workers: Swedish measurement data and exposure assessment. J Occup Environ Med. 59(12):e327-e341.

RESPONSE*: This comment refers to Table 2-4 in section 2.1 (Introduction). The studies listed have been reviewed and those that discuss cancer effects have been included in Chapter 2 Section 19 (Cancer).*

COMMENT: Suggestion to include Sauni et al (2017) Sauni R, Oksa P, Uitti J, Linna A, Kerttula R, Pukkala E. 2017. Cancer incidence among finnish male cobalt production workers in 1969-2013: A cohort study. BMC Cancer. 17(1):340.

RESPONSE*: This comment refers to Table 2-4 in section 2.1 (Introduction). The studies that examine cancer as an endpoint are included in Chapter 2 Section 19 (Cancer).*

COMMENT: Hardmetal cancer cohorts also included non-cancer outcomes, e.g. non-malignant respiratory disease

RESPONSE*: This comment refers to Table 2-4 in section 2.1 (Introduction). The non-cancer outcomes from hard metal cancer cohorts have been included as appropriate.*

The following text was added to Chapter 2 section 2.4 Respiratory: "Respiratory effects of exposure to cobalt, tungsten, and nickel were evaluated in an international cohort of hard metal production workers (Marsh et al. 2017a; Marsh et al. 2017b).Workers from 3 companies, 17 sites among 5 countries, including the United States, Austria, Germany, Sweden, and the United Kingdom were evaluated. Information on respiratory parameters were obtained from various national datasets, and phone interviews were completed for participants when possible. These interviews provided information on demographic and lifestyle factors. The exposed workers showed chronic obstructive pulmonary disease, bronchitis, emphysema, and asthma (Marsh et al. 2017a; Marsh et al. 2017b)."

The following text was added to Chapter 2 section 2.5 Cardiovascular "Cardiovascular effects of exposure to cobalt, tungsten, and nickel were evaluated in an international cohort of hard metal production workers (Marsh et al. 2017a; Marsh et al. 2017b).Workers from 3 companies, 17 sites among 5 countries, including the United States, Austria, Germany, Sweden, and the United Kingdom were evaluated. Information on cardiovascular parameters were obtained from various national datasets, and phone interviews were completed for participants when possible. These interviews provided information on demographic and lifestyle factors. The exposed workers showed increased incidences of cardiovascular diseases as a result of occupational exposure (Marsh et al. 2017a; Marsh et al. 2017b)."

COMMENT: In the Finnish factory described by Linna and Sauni, also co-exposure to irritant gases in some departments.

RESPONSE*: This comment refers to the following sentence in section 2.4 (Respiratory): "In the studies detailed above, all the factory workers were subjected to co-exposures with other metals like nickel and chromium, therefore the health effects observed might not be caused by cobalt alone." The suggested edit was included and the sentence now reads: "In the studies detailed above, all the factory workers were subjected to co-exposures with other metals like nickel and chromium and irritant gases, therefore the health effects observed might not be caused by cobalt alone."*

COMMENT: Nor was there a correlation between cobalt exposure and respiratory effects on an individual level within this group (correlations occurred only on a group level: low, high, control)

RESPONSE*: This comment refers to the following sentence in section 2.4 (Respiratory): "While the respiratory effects appear at a greater rate in individuals who were exposed to higher concentrations of Co, the study does not provide any information on the smoking status of individuals in this treatment group." The comment was included as a new sentence: "There was no correlation between cobalt exposure and respiratory effects on an individual level within this group, correlations occurred only on a group level: low, high, control."*

COMMENT: Days?

RESPONSE*: This comment refers to the following sentence in section 2.9 (Hepatic): "Necrosis and congestion of the liver were observed in both F344/N rats and B6C3F1 mice that died following intermittent exposure to 19 mg Co/m3 as cobalt sulfate over 16." The word "days" was added to clarify and the sentence now reads: "Necrosis and congestion of the liver were observed in both F344/N rats and B6C3F1 mice that died following intermittent exposure to 19 mg Co/m3 as cobalt sulfate over 16 days."*

COMMENT: Move to 2.12. ocular

RESPONSE*: This comment refers to the following sentence in section 2.13 (Endocrine): "Acute-duration exposure by a single subcutaneous injection to 45 mg Co/kg as dicobalt octacarbonyl did not cause ocular effects in guinea pigs (species not specified)." The suggested edit was included and the sentence was moved to section 2.12.*

COMMENT: It may be relevant to introduce the -in my view- key effect of cobalt ion here: Hematological effect, as a consequence of cobalt-related hypoxia mimicry.

RESPONSE*: This comment refers to section 2.18 (Other Noncancer). Other non-cancer effects are used to include any effect (e.g., alterations in blood glucose levels) not covered in the systems listed from 2.1 to 2.17. Hematological effects, as a consequence of cobalt-related hypoxia mimicry are briefly discussed in Chapter 2 Section 21 (Mechanism of Action).*

COMMENT: Should this read "no positive studies were identified" (i.e., studies demonstrating increased incidences of cancer in humans following exposure to cobalt by oral, dermal or inhalation route). There are several cancer cohorts from cobalt exposed workers, some from the hard metal industry (e.g. Marsh et al 2017), or from the cobalt industry (Sauni, 2017); or the older studies from electrochemical plants in France (Mur, Moulin).

RESPONSE*: This comment refers to the following sentence in section 2.19 (Cancer): "No studies were identified that examined cancer in humans following inhalation, oral, or dermal exposure to cobalt." The suggested edit was included and the sentence now reads: "No studies were identified that reported significant cancerous effects in humans following inhalation, oral, or dermal exposure to cobalt."*

COMMENT: Suggestion to re-check the calculation from the CoSO4-heptahydrate to Co concentrations: The NTP concentration for the Co sulfate of 0.3, 1 and 3 correspond, in my view, to 0.063, 0.21 and 0.63 Co adjusted for the Co content of approx. 21% cobalt in Co SO4.7(H2O). or, in case the hexahydrate is assumed to have been formed in the inhalation atmosphere, then the Co content would be 22.4%.

RESPONSE*: This comment refers to the following sentence in section 2.19 (Cancer): "Increased incidence of alveolar/bronchiolar neoplasms was noted following lifetime exposure of male rats to 1.14 mg cobalt/m3 and in female F344/N rats exposed to 0.38 mg cobalt/m3." The calculations were rechecked and the concentrations were updated throughout the profile, applicable LSE figures and tables, and applicable MRL worksheets in Appendix A of the profile.*

COMMENT: General comment on Genotoxicity section: a reference that is, in my view, a key reference is missing: Kirkland et al, 2015. New investigations into the genotoxicity of cobalt compounds and their impact on overall assessment of genotoxic risk - PubMed (nih.gov). This publication contains many high-quality studies that were conducted by the cobalt industry for compliance with REACH. All of the studies in this publication are highly reliable due to their GLP and OECD-guideline compliance status. The publication puts the findings into context with other findings in the public domain and is therefore often mistaken to be a review. I highly recommend inclusion of these original data.

RESPONSE*: This comment refers to section 2.20 (Genotoxicity). The results from this study were included in the profile.*

COMMENT: Spell out SSB

RESPONSE*: This comment refers to the following sentence in section 2.20 (Genotoxicity): "Hengstler et al. (2003) showed a correlation between increased air concentration of cobalt and levels of DNA- SSB." The full name was spelled out and the sentence now reads: "Hengstler et al. (2003) showed a correlation between increased air concentration of cobalt and levels of single stranded DNA binding protein (DNA-SSB)."*

COMMENT: Can / may

RESPONSE*: This comment refers to the following sentence in section 2.21 (Mechanism of Action): "While the exact mechanism(s) for the transport of cobalt cations through cellular membranes are unknown, the natural resistance-associated macrophage protein 2 (NRAMP 2)/divalent metal transporter 1 (DMT1) <u>can</u> play role in this transport (Forbes and Gros 2003)." The suggested edit was included and the sentence now reads: "While the exact mechanism(s) for the transport of cobalt cations through cellular membranes are unknown, the natural resistance-associated macrophage protein 2 (NRAMP 2)/divalent metal transporter 1 (DMT1) can play role in this transport (Forbes and Gros 2003)."*

COMMENT: Suggestion to replace with "measured", as these were empirical data.

RESPONSE*: This comment refers to the following sentence in section 3.1.1 (Absorption): "Danzeisen et al. (2020) calculated measured the bioavailability of cobalt chloride ($CoCl_2$), cobalt tetraoxide (Co_3O_4),*

cobalt sulfide (CoS), and lithium cobalt oxide ($CoLiO_2$) in male and female rats." The word "calculated" was replaced with "measured" and the sentence now reads: "Danzeisen et al. (2020) measured the bioavailability of cobalt chloride ($CoCl_2$), cobalt tetraoxide (Co_3O_4), cobalt sulfide (CoS), and lithium cobalt oxide ($CoLiO_2$) in male and female rats."

COMMENT: "Solubilities" is repetitive; perhaps "bioaccessibilities"?

***RESPONSE**: This comment refers to the following sentence in section 3.1.1 (Absorption): "Danzeisen et al. (2020) evaluated the solubility of various cobalt compounds in both simulated gastric and intestinal fluid and reported that the solubilities varied by 100-fold in gastric fluid and more than 1000-fold in intestinal fluid with the more soluble compounds having the highest solubilities." The sentence was revised and now reads: "Danzeisen et al. (2020) evaluated the solubility of various cobalt compounds in both simulated gastric and intestinal fluid and reported that the solubilities varied by 100-fold in gastric fluid and more than 1000-fold in intestinal fluid with the more soluble compounds being more bioaccessible."*

COMMENT: Error in original publication, see Corrigendum to: "Bioelution, Bioavailability, and Toxicity of Cobalt Compounds Correlate" (nih.gov)

***RESPONSE**: This comment refers to Table 3-6 in section 3.1.4 (Excretion). The Co chloride values in the table were changed to 2.48 based on the suggested source.*

COMMENT: Change order to match wording slow, medium, fast

***RESPONSE**: This comment refers to the following sentence in section 3.1.5 (Physiologically Based Pharmacokinetic/Pharmacodynamic Models): "Elimination from tissue compartments is described by three first order rate constants representing slow, medium, and fast elimination pools with half-times of 6, 60, and 800 days, respectively." The suggested edit was included and the sentence now reads: "Elimination from tissue compartments is described by three first order rate constants representing slow, medium, and fast elimination pools with half-times of 800, 60, and 6 days, respectively."*

COMMENT: Statement incorrect, compare with sentence above of half-life of 5.27 year of 60Co. Adjust statement.

***RESPONSE**: This comment refers to the following sentence in section 4.1 (Chemical Identity): "All cobalt isotopes have half-life less than 24 hours." The sentence has been revised to say that cobalt isotopes have half-lives of varying lengths, but most are less than 24 hours: "Cobalt isotopes have half-lives that are specific to the isotope , but most are less than 24 hours (NNDC 2021)."*

COMMENT: Check if this is correct – seems too high. Based on abstract of cited study, there were 9.4 ng Co/g food, and an average estimated intake of 11 ug Co/day.

***RESPONSE**: This comment refers to the following sentence in section 5.6 (General Population Exposure): "Dabeka and McKenzie (1995) estimated that the dietary cobalt intake by Canadian children ages 1–19 ranged from 7 to 14 mg/day." The units were updated from mg/day to µg/day and the sentence now*

reads: "Dabeka and McKenzie (1995) estimated that the dietary cobalt intake by Canadian children ages 1–19 ranged from 7 to 14 µg/day."

COMMENT: Unclear why human cancer cohorts are not represented.

***RESPONSE**: Figure 6-1 was updated to include cancer cohorts.*

COMMENT: As a sub-chronic rodent study considering using Danzeisen et al (2020), where lower doses were applied and no-effect levels were observed, as well as dose response for hematological effects and body weight effects.

***RESPONSE**: Noted and study included in Chapter 2 where health effects are discussed. The following text was added to Chapter 2 Section 3 Body Weight effects "The body weight at autopsy was reduced by 11% (males) and 9% (females), respectively, at 7.44mg Co (as CoCl2)/kg bw/day. At the end of the 4-week recovery period (test day 118), the body weight of the male and female animals exposed to the highest dose was still reduced by 17% or by 13%, respectively, compared with the control group (Danzeisen et al. 2020). Danzeisen et al. (2020) also examined the effects of oral exposure to Co3O4 at the dose of 734 mg Co/kg/day for 90 days and observed there were marginal effects on body weight in male and female rats.".*

Additionally, the following was included in Chapter 2 Section 7 Hematological health effects "Intermediate-duration oral exposure to cobalt caused hematological effects in rats and mice. Rats were exposed to 0.74, 2.48, and 7.44 mg Co/kg/day as cobalt chloride hexahydrate orally daily for 90 days (Danzeisen et al. 2020). In this study, male rats showed no alterations in hematological parameters at 0.74 mg Co/kg/day; however, at a dose of 2.48 mg Co/kg day there was a 10.7%, 9.2%, and 10.2% increase in hemoglobin, erythrocytes, and hematocrit respectively. While the male rats were more sensitive and showed changes in hematological parameters at lower doses, female rats showed an increase of 13.4% and 9.8% in hemoglobin and erythrocytes, respectively, only at a dose of 7.44 mg Co/kg/day (Danzeisen et al. 2020). Danzeisen et al. (2020) also examined effects of Co_3O_4 on hematological parameters. They observed that a daily oral dose of 220 mg Co/kg/day increased hemoglobin, erythrocytes, and hematocrit by 9.5%, 9.6%, and 9.2%, respectively, in male rats, and a 5.9% increase in hemoglobin level in female rats. At the highest dose of 734 mg Co/kg/day, males and female rats showed an increase in hemoglobin (25.4% males and 16.4% females), erythrocytes (22.7% males and 12.9% females), and hematocrit (24.2% males and 13.9% females) (Danzeisen et al. 2020)"

COMMENT: Reviewer 2: Sauni et al 2017, cancer cohort is missing. No co-exposure to hardmetal of diamond tools in Sauni cohort

***RESPONSE**: As per ATSDR guidelines detailed in "Guidance for the Preparation of Toxicological Profiles", MRLs are not based on cancer studies and therefore are not included here.*

COMMENT: Inflammation ?

***RESPONSE**: Edited to correct infection to inflammation. Text was updated to read as follows "Animal studies showed changes in lung weight, lung inflammation, edema, congestion, and bronchitis after acute-duration exposure."*

COMMENT: Unclear why Sauni and Marsh of 2017 are missing. Large cohorts with more than 500,000 person-years.

RESPONSE: *Sauni et al. 2017 and Marsh et al. 2017 are cancer cohorts and are discussed in Chapter 2. Section 19. Sauni et al. 2017 and March et al. 2017 are cancer studies and ATSDR does not develop an MRL based on cancer incidence.*

Sauni et al 2010 details incidences of asthma when workers were co-exposed to sulphur dioxide and ammonia. In the absence of these irritant gases (sulphur dioxide and ammonia), the cases of asthma decreased drastically, suggesting these effects may have been caused by the irritant gases and not cobalt alone. This discussion is included in the Chronic MRL inhalation section of the toxicological profile. These details are also included in Chapter 2, Section 4 of the profile.

COMMENT: General comment on MRL development: seeing that Co ion is not further metabolized by mammals or humans, the AF of 10 for intraspecies differences should be reduced, see e.g. ECETOC (2003) ECETOC-TR-086.pdf.

I question the choice of studies for the inhalation interim exposure duration; I haveh pointed towards the work by Sauni (2010 and 2017) earlier in the document.

Also, it may be worthwhile to look at the 90-day exposure in rats by us (Danzeisen et al) for subchronic effects where a NOAEL and LOAEL has been established on haematological effects, and use this as a bases for a human MRL. This was done to derive DNELs (oral exposure) for the general population for cobalt under REACH. If of interest, I can provide the DNEL calculation.

RESPONSE*: The UFs used to derive an MRL are based on ATSDR guidelines outlined in "Guidance for the Preparation of Toxicological Profiles".*

Sauni et al. 2010 details incidences of asthma when workers were co-exposed to sulphur dioxide and ammonia. In the absence of these irritant gases (sulphur dioxide and ammonia), the cases of asthma decreased drastically, suggesting these effects may be caused by the irritant gases and not cobalt alone. This discussion is included in the Chronic MRL inhalation section of the toxicological profile. Sauni et al. 2017 is a cancer study and ATSDR does not develop MRLs based on cancer incidence.

Danzeisen et al . (2020) lends very strong support to ATSDR's derived MRL. The study details are included in the intermediate-duration oral MRL section of the toxicological profile.

Comments provided by Peer Reviewer #3

ATSDR Charge Questions and Responses

Chapter 1. Relevance to Public Health

QUESTION: Do you agree with those effects known to occur in humans as reported in the text? If not, please explain why and provide a copy of additional references you would cite and indicate where (in the text) these references should be included.

COMMENT: I agree with the effects reported

RESPONSE: *No response needed.*

QUESTION: Are the effects only observed in animals likely to be of concern to humans? Why or why not? If you do not agree, please explain.

COMMENT: The effects seen in animals are relevant. There is overlap between organ systems affected and main clinical outcomes seen in humans and other mammals.

RESPONSE: *No response needed.*

QUESTION: Have exposure conditions been adequately described? If you disagree, please explain

COMMENT: They have been adequately described.

RESPONSE: *No response needed.*

Minimum Risk Levels (MRLs)

QUESTION: If no MRLs have been derived, do you agree that the data do not support such a derivation? Please explain.

COMMENT: I agree that an MRL can not be derived for the acute inhalation MRL. I do not agree that an intermediate inhalation MRL can't be derived given the finding that multiple studies report effects (primrly respiratory) in rodents exposed to cobalt at a relevant duration. The NTP study provides a NOAEL – this NOAEL was seen in both the shorter term and chronic duration studies.

RESPONSE: *Although multiple studies report respiratory effects, the NOAELs from these studies are at concentrations where cancer effects are also observed. In the NTP 1991 study, the NOAEL for respiratory effects also causes cancer at the same dose. ATSDR considers cancer a serious effect, and therefore would not derive an MRL from this dose in accordance with ATSDR's latest "Guidance for the Preparation of Toxicological Profiles" document.*

QUESTION: If MRLs have been derived, do you agree with the proposed MRL values? Explain. If you disagree, please specify the MRL value that you would propose.

COMMENT: I agree with the chronic inhalation MRL.

RESPONSE: *No response needed.*

QUESTION (Subset of preceding question): Do you agree/disagree with each component of the total uncertainty factor? Explain. If you disagree, please specify the uncertainty factor(s) that you propose.

COMMENT: I agree with the UF used for the chronic inhalation MRL. Consider taking the Awoyemi et al. (2017) study through a calculation based on the NOAEL for deriving the acute oral MRL. These values could be very similar and add additional weight to the value you have derived.

RESPONSE: *The doses used in Awoyemi et al. (2017) were 6 and 11 mg Co/kg/day and hematological effects were observed at 11 mg Co/kg/day. The study identified a NOAEL of 6 mg Co/kg/day which was deemed to be too high for human exposures. Additional details regarding the derivation of MRLs are included in Appendix A. ATSDR Minimal Risk Levels And Worksheets.*

QUESTION (Subset of preceding question): Please comment on any aspect of our MRL database assessment that you feel should be addressed.

COMMENT: For the acute intermediate oral MRL I questioned whether alternative studies have been adequately assessed. Davis and Fields (1958) has several high risk of bias concerns that may suggest that a higher quality study may be more appropriate. It is also unclear to me that this study was blinded. Page C-7 states that:

a. After the risk of bias questionnaires were completed for the health effects studies, the studies were assigned to one of three risk of bias tiers based on the responses to the key questions listed below and the responses to the remaining questions.

i. Is there confidence in the exposure characterization? (only relevant for observational studies)

ii. Is there confidence in the outcome assessment?

iii. Does the study design or analysis account for important confounding and modifying variables? (only relevant for observational studies)

First Tier. Studies placed in the first tier received ratings of "definitely low" or "probably low" risk of bias on the key questions AND received a rating of "definitely low" or "probably low" risk of bias on the responses to at least 50% of the other applicable questions.

1. Note that several studies including Davis and Fields (1958) has a high RoB for one of these key domains (i.e., high RoB for Is there confidence in the exposure characterization? This is concerning for anu study (not just an observational study). It's unclear why this high RoB concern is ignored for these older studies. Indeed the description o fthis study shows that multiple assumptions were needed to estimate the exposure (including the use of a 70 kg adult that may or may not be appropriate for US adults living in the late 1950s when this study was performed).

RESPONSE: *The literature review did not identify any newer studies where humans were exposed to cobalt orally for acute and intermediate durations. Based on the systematic review described in Appendix C, all studies on oral acute- and intermediate- duration exposures were placed in the first tier for Risk of Bias analysis. The weight of 70 kg for an adult was based on the guidelines from EPA's Exposure*

Scenario Selection. Additionally, one new animal study involving oral exposure for an intermediate duration was identified which adds strong support to the derived MRL from Davis and Fields (1958). The DNEL derived by the Cobalt REACH Consortium using the doses from Danzeisen et al. (2020) and MRL from Davis and Fields (1958) result in a similar value. The DNEL derived value is effectively identical to ATSDR's intermediate-duration oral MRL (0.03 mg/k/d for the MRL and 0.0298 mg/kg/d for the DNEL which can be rounded to 0.03 mg/k/d).

Chapter 2. Health Effects

QUESTION: Do the health effect conclusions made in Chapter 2 adequately reflect the findings in the published literature? If not, please suggest appropriate changes.

COMMENT: Descriptions are adequate.

RESPONSE: *No response needed.*

QUESTION: Were adequately designed human studies identified in the text (i.e., good exposure data, sufficiently long period of exposure to account for observed health effects, adequate control for confounding factors)? Were the major study limitations sufficiently described in the text without going into lengthy discussions? If study limitations were not adequately addressed, please suggest appropriate changes.

COMMENT: Study limitations are incompletely discussed here – these should be addressed in the studies considered for deriving the MRLs.

RESPONSE: *The following text was included for respiratory effects that address the limitations of these studies that were considered for deriving an MRL.*

Respiratory-

"Sauni et al. (2010) conducted a case study of occupational asthma in cobalt plant workers in Finland from 1967 -2003 where the mean air concentrations of cobalt in different departments ranged from 0.03 to 0.15 mg/m3. Until 1987, cobalt was being produced from pyrite oar concentrate which led to co-exposures with irritant gases like sulfur dioxide (SO_2) and ammonia (NH_3) that are known respiratory irritants (Andersson et al. 2006; ATSDR 1998; Huber and Loving 1991). After 1987, cobalt was produced using by-products of the metallurgic industry as raw material which eliminated the co-exposure to the irritant gases and notably, the incidence of asthma decreased to only 1 case (compared to 21 cases of asthma observed between years 1967-1987). Therefore, it is likely that the health effects observed in this study were due to the co-exposure to sulfur dioxide and ammonia and not cobalt alone."

"In this study by Gennart and Lauwerys (1990), cobalt air concentrations were measured from 2 rooms that workers moved freely between during the work shift and no individual worker stay times or exposures were provided. The absence of this information did not allow accurate estimation of the average exposure per worker."

Hematological-

"The NOAEL dose of 6 mg Co/kg/day used in Awoyemi et al (2017) where no effects were observed is a dose that is rather high for humans to be exposed to cobalt via oral exposure. The average daily intakes are often in the microgram range."

"Krasovskii and Fridyland (1971) exposed groups of rats to 0, 0.05, 0.5 and 2.5 mg Co/kg/day as cobaltous chloride, daily for 7 months. The group treated with 2.5 mg Co/kg/day showed a persistent increase in erythrocytes, the 0.5 mg Co/kg/day group showed a transient increase, and the lowest exposure group showed no effect. This study provided qualitative findings but did not report numerical data and their statistical significance."

QUESTION: Were adequately designed animal studies identified in the text (i.e., adequate number of animals, good animal care, accounting for competing causes of death, sufficient number of dose groups, and sufficient magnitude of dose levels)? If not, does the inadequate design negate the utility of the study? Please explain.

COMMENT: Animal studies were adequate.

RESPONSE: *No response needed.*

QUESTION: Were the animal species appropriate for the most significant toxicological endpoint of the study? If not, which animal species would be more appropriate and why?

COMMENT: Most cited studies used rodents, this species is relevant for hazard identification.

RESPONSE: *No response needed.*

QUESTION: Has adequate attention been paid to dose-response relationships for both human and animal data? Please explain.

COMMENT: Descriptions are adequate.

RESPONSE: *No response needed.*

QUESTION: Are you aware of any studies that are not included in the profile that may be important in evaluating the toxicity of the substance? Please provide a copy of each study and indicate where in the text each study should be included.

COMMENT: I am unaware of additional studies

RESPONSE: *No response needed.*

QUESTION: Are you aware of any studies that are not included in the profile that may be relevant to deriving MRLs for any of the substance isomers? Please provide a copy if this is a new reference.

COMMENT: I am unaware of additional studies**.**

RESPONSE: *No response needed.*

QUESTION: Were all appropriate NOAELs and/or LOAELs identified for each study (both in the text and the Levels of Significant Exposure (LSE) tables and figures)? If not, did the text provide adequate

justification for excluding NOAELs/LOAELs including, but not limited to, citing study limitations? Please suggest appropriate changes.

COMMENT: Appropriate NOAELs and LOAELs were cited.

RESPONSE: *No response needed.*

QUESTION: Do you agree with the categorization of "less serious" or "serious" for the effects cited in the LSE tables? If not, please explain why and suggest appropriate changes.

COMMENT: I agre**e.**

RESPONSE: *No response needed.*

QUESTION: Have all possible mechanisms of action been discussed within their relevant health effect section? If not, please explain. If citing a new reference, please provide a copy and indicate where (in the text) it should be included.

COMMENT: Appears complete, however, it is unclear at times which mechanisms have been observed in vivo (vs. in vitro studies).

RESPONSE: *Added language to Chapter 2, Section 21, Mechanism of Action, to clarify which model the mechanisms have been observed in. Specific cell line or animal models used are denoted appropriately in this section.*

Added the following text in the profile:

- *"…Calcium influx in cells is known to be altered by soluble cobalt when it blocks the inorganic calcium channels in cells harvested from rodent models…"*
- *"…The ubiquitous calcium channels in liver cells harvested from rats (Yamatani et al. 1998) and pancreatic cells harvested from mice (Henquin and Lambert 1975)…"*
- *"…Leydig cells in a rodent model…"*
- *"…Hypoxia can also be observed in other tissues such as cardiac, brain, liver, and renal from rats and mice…"*
- *"…DNA repair in human fibroblasts…"*
- *"...damage in a mouse model and human lung fibroblast cells…"*
- *"…increase oxidative damage in in vivo animal models…"*

QUESTION: Are the conclusions appropriate given the overall database? If not, please discuss your own conclusions based on the data provided and other data provided to you but not presented in the text.

COMMENT: Conclusions are appropriate.

RESPONSE: *No response needed.*

QUESTION: RADIOACTIVE COBALT STUDIES: Are you aware of any studies using radioactive cobalt isotopes that would improve the information presented in this chapter.

COMMENT: I am unaware of additional studies.

RESPONSE: *No response needed.*

QUESTION: NANOPARTICLES: Is the section regarding cobalt nanoparticles appropriately detailed and accurate? If not, please identify its shortcomings, recommend topics to include, identify where those topics should be addressed in the text, and provide copies of the new references supporting those topics.

COMMENT: This discussion is adequate and appears complete.

RESPONSE: *No response needed.*

Chapter 3. Toxicokinetics, Susceptible Populations, Biomarkers, Chemical Interactions

QUESTION: Is there adequate discussion of absorption, distribution, metabolism, and excretion of the substance? If not, suggest ways to improve the text.

COMMENT: The text implies that absorption has been evaluated directly – instead values for absorption of nonradiolabeled cobalt have largely been presumed based on urinary excretion. This could be made more clear.

RESPONSE: *"Values for non-radiolabeled cobalt have been calculated based on urinary excretion of cobalt." Has been included in the profile in Chapter 3.*

QUESTION: Have all available pharmacokinetic/pharmacodynamic models and supporting data been presented? If not, please explain.

COMMENT: Adequately described.

RESPONSE: *No response needed.*

QUESTION: Is there adequate discussion of the differences in toxicokinetics between humans and animals? Is there adequate discussion of the relevance of animal toxicokinetic information for humans?

COMMENT: Adequately described.

RESPONSE: *No response needed.*

QUESTION: Are there any data relevant to child health and developmental effects that have not been discussed in the profile and should be? Please provide any relevant references.

COMMENT: I am unaware of additional studies.

RESPONSE: *No response needed.*

QUESTION: Is there a discussion of populations at higher risk of susceptibility? Do you agree with the choice of populations? Please explain and provide any additional relevant references.

COMMENT: This section is adequate as well.

RESPONSE: *No response needed.*

QUESTION: Are the biomarkers of exposure specific for the substance? Please explain.

COMMENT: Yes – based on direct measurement of cobalt.

RESPONSE: *No response needed.*

QUESTION: Are the biomarkers of effect specific for the substance? Please explain.

COMMENT: No specific biomarkers of effect – this was adequately discussed in the draft document.

RESPONSE: *No response needed.*

QUESTION: Is there adequate discussion of the interactive effects with other substances? Does the discussion concentrate on those effects that might occur at hazardous waste sites? Please explain and provide any additional references.

COMMENT: I am unaware of additional studies. The discussion of EDTA (and other chelators) seems too brief given the extent to which these interactions are discussed later in the document.

RESPONSE: *Chelators like EDTA are discussed only with respect to how cobalt interacts with them. Chapter 3, Section 4, Interactions with other chemicals, focuses on identifying what chemicals cobalt interacts with and the effects this interaction may have on organ system(s). In this profile, these chelators are mitigating effects of health impacts caused due to cobalt toxicity which are identified only in 3 studies.*

QUESTION: If interactive effects with other substances are known, does the text discuss the mechanisms of these interactions? Please explain and provide any additional references.

COMMENT: I am unaware of additional studies. Mechanisms have been incompletely described. Based on cobalt interactions with metal transporters there are likely additional metal-metal interactions (e.g., manganese) since the DMT transporters are involved with multiple metals.

RESPONSE: *There were no additional interaction studies that were identified in the literature search. Additionally, this profile focuses on interactions of cobalt with DMT transporters and thus other metal-metal interactions that do not include cobalt are not included.*

Chapter 4. Chemical and Physical Information

QUESTION: Are any of the values or information provided in the chemical and physical properties tables wrong or missing? Please explain and provide any additional references.

COMMENT: I spot checked some values that were derived correctly from cited sources.

RESPONSE: *No response needed.*

QUESTION: Is information provided on the various forms of the substance? Please explain.

COMMENT: Yes, different forms of cobalt have data available.

RESPONSE: *No response needed.*

Chapter 5. Potential for Human Exposure

QUESTION: Is the information on production, import/export, use, and disposal of the substance complete? Please explain and provide any additional relevant references.

COMMENT: This appears complete.

RESPONSE: *No response needed.*

QUESTION: Has the text appropriately traced the substance from its point of release to the environment until it reaches the receptor population? Does the text provide sufficient and technically sound information regarding the extent of occurrence at NPL sites? Do you know of other relevant information? Please provide references for added information.

COMMENT: This appears complete.

RESPONSE: *No response needed.*

QUESTION: Does the text cover pertinent information relative to transport, partitioning, transformation, and degradation of the substance in all media? Do you know of other relevant information? Please provide references for added information.

COMMENT: This appears complete. I am unaware of additional studies.

RESPONSE: *No response needed.*

QUESTION: Does the text provide information on levels monitored or estimated in the environment, including background levels? Are proper units used for each medium? Does the information include the form of the substance measured? Is there an adequate discussion of the quality of the information? Do you know of other relevant information? Please provide references for added information.

COMMENT: This appears complete. Proper units are used. Quality is not addressed per se (no formal quality assessment). I am unaware of additional studies.

RESPONSE: *No response needed.*

QUESTION: Does the text describe sources and pathways of exposure for the general population and occupations involved in the handling of the substance, as well as populations with potentially high exposures? Do you agree with the selection of these populations? If not, why? Which additional populations should be included in this section?

COMMENT: This appears complete. I agree with the selection of populations.

RESPONSE: *No response needed.*

Chapter 6. Adequacy of the Database

QUESTION: Do you know of other studies that may fill a data gap? Please provide any relevant references.

COMMENT: I am unaware of additional studies.

RESPONSE: *No response needed.*

QUESTION: Do you agree with the identified data needs? Please explain.

COMMENT: These are relatively generic – it is unclear to what extent if any these would affect derivation of the MRL. I'd prefer a more focused discussion of "true" needs for hazard assessment.

RESPONSE: *This section has been developed based on ATSDR guidelines outlined in " Guidance for the Preparation of Toxicological Profiles".*

QUESTION: Are the data needs presented in a neutral, non-judgmental fashion? Please note any bias in the text.

COMMENT: I did not detect bias in the draft document.

RESPONSE: *No response needed.*

Chapter 7. Regulations and Guidelines

QUESTION: Are you aware of any additional regulations or guidelines that should be included? Please provide citations.

COMMENT: This section appers complete.

RESPONSE: *No response needed.*

QUESTION: Are there any that should be removed? Please explain.

COMMENT: The list should not be amended.

RESPONSE: *No response needed.*

Additional References from Reviewer*

**These are references cited within the reviewer's individual comments. Responses to the reviewer's comments specify the disposition of these references within the toxicological profile.*

Appendices

QUESTION: Please provide any comments on the content, presentation, etc. of the included appendices.

COMMENT: *No response provided.*

RESPONSE: *No response needed.*

Annotated Comments on the Profile

COMMENT: Describe what is meant by properties: physicochemical? Metallurgical? Enzymatic?

RESPONSE*: This comment refers to the following sentence in section 1.1 (Overview and U.S. Exposures): "Cobalt and cobalt compounds are naturally occurring and have properties similar to those of iron and nickel." The sentence has been updated to specify that the properties are physicochemical: "Cobalt and cobalt compounds are naturally occurring and have similar physicochemical properties to those of iron and nickel."*

COMMENT: Correct spelling for cyanocobalamin

RESPONSE*: This comment refers to the following sentence in section 1.1 (Overview and U.S. Exposures): "The biochemically relevant form of cobalt is vitamin B_{12}, also known as cyanocobalmin, which plays a crucial role in maintaining optimal health in humans and animals." The spelling has been fixed and the sentence now reads: "The biochemically relevant form of cobalt is vitamin B_{12}, also known as cyanocobalamin, which plays a crucial role in maintaining optimal health in humans and animals."*

COMMENT: Identify chemical form used by NTP

RESPONSE*: This comment refers to the following sentence in section 1.2 (Summary of Health Effects): "No studies were identified that examine carcinogenic effects in humans after inhalation exposure, however animal studies reported carcinogenicity in rats and mice of both sexes after inhalation exposure (NTP 1991,2014)." These chemical forms are identified and discussed in detail in Chapter 2, Section 19.*

COMMENT: Is there direct in vivo evidence to support this statement?

RESPONSE*: This comment refers to the following sentence in section 1.2 (Summary of Health Effects): "Cobalt ion in the body gives rise to inhibition of DNA repair, genotoxicity, and generation of reactive oxygen species (ROS) resulting in oxidative damage by cobalt." Evidence is discussed in detail in Chapter 2 Section 21. No edits needed here.*

COMMENT: Human data available – why not "known"? It is unclear what criteria were used to reach a final hazard conclusion.

RESPONSE*: This comment refers to the following bullet in section 1.2 (Summary of Health Effects): "Hematological effects are a presumed health effect of oral exposure to cobalt." This rating is based on the systematic review process which is detailed in Appendix C of the toxicological profile. The criteria to reach this conclusion are based on the ATSDR guidelines found in Guidance for the Preparation of Toxicological Profiles (cdc.gov). No edits needed.*

COMMENT: Indicate that this refers to intermediate duration of exposure

RESPONSE*: This comment refers to the following bullet in section 1.2 (Summary of Health Effects): "Intermediate inhalation of cobalt resulted in lesions and degermation in respiratory tract." The suggested edit was included and the sentence now reads: "Intermediate-duration cobalt inhalation resulted in lesions and degeneration in the respiratory tract."*

COMMENT: Define "human controled occupational studies" – or do you mean controlled or occupational studies?

RESPONSE*: This comment refers to the following bullet in section 2.1 (Introduction): "There are few human controlled occupational studies." The sentence has been edited for clarity and now reads: "There are few human studies that include control groups and occupational studies that examine health effects of exposure to cobalt."*

COMMENT: Was absorption measured or inferred from changes in urinary cobalt excretion. Here and elsewhere provide chemical form/salt of the cobalt.

RESPONSE*: This comment refers to the following bullet in section 2.1 (Introduction): "Inhaled cobalt in humans was absorbed in the lungs and was associated with increases in chronic phlegm and decreases in spirometric parameters." Absorption was quantified based on the urinary levels in the study. The chemical form and salts used in each study are detailed in each section in Chapter 2 from Section 2.2 Death to Section 2.22 Cobalt nanoparticles along with health effects. No edits needed.*

COMMENT: Define IEI.

RESPONSE*: This comment refers to the following sentence in section 2.1 (Introduction): "In the study by Lantin et al. (2011), IEI was significantly (P< 0.001) correlated with mean corpuscular hemoglobin*

concentration (MCHC) in both univariate and multivariate regression analyses but there was no significant relationship between the IEI and the red cell count (polycythemia) even after occupational exposure to inhaled cobalt." The full name was included and the sentence in Chapter 2, Section 1 Introduction now reads: "In the study by Lantin et al. (2011), the integrated exposure index (IEI) was significantly (P< 0.001) correlated with mean corpuscular hemoglobin concentration (MCHC) in both univariate and multivariate regression analyses, but there was no significant relationship between the IEI and the red cell count (red cell count was not affected) even after occupational exposure to inhaled cobalt."

COMMENT: Indicate these represent high dose acute and intermediate duration exposures. Similar comment on line 25 same page

***RESPONSE**: This comment refers to the following sentence in section 2.2 (Death): "In laboratory animal studies, acute- and intermediate-duration exposure to cobalt appeared to cause mortality but chronic-duration exposure to lower concentrations had no effect on survival." The suggested edit was included and the sentence now reads: "In laboratory animal studies, high dose acute- and intermediate-duration exposure to cobalt appeared to cause mortality but chronic-duration exposure to lower concentrations had no effect on survival."*

COMMENT: Mini-pigs were used – these are Sus domesticus. Provide chemical form of cobalt used. Same page line 19 – why is there a question about species of guinea pig used (vs strain)? This notation (species not specified) appears in multiple locations.

***RESPONSE**: This comment refers to the following sentence in section 2.3 (Body Weight): "A 3-month exposure to cobalt for 5 days a week, 6 hours/day metal at 0.1 mg Co/m3 resulted in a 16% decrease in body weight in pigs (species not specified)." Because the study does not specify the strain, the text was updated to indicate this every time the study is referenced: "A 3-month exposure to cobalt metal for 5 days a week, 6 hours/day at 0.1 mg Co/m3 resulted in a 16% decrease in body weight in pigs (strain not specified)."*

COMMENT: I presume the guideline relates to biologically significant results (i.e., change this to:…which is not considered biologically significant…

***RESPONSE**: This comment refers to the following sentence in section 2.3 (Body Weight): "Elbetieha et al. (2008) demonstrated that a 12 week exposure to 23 mg Co/kg/day as cobalt chloride hexahydrate induced a significant 7% increase of body weight in Swiss mice, which is not considered significant based on ATSDR guidelines." The suggested edit was included and the sentence now reads: "Elbetieha et al. (2008) demonstrated that a 12 week exposure to 23 mg Co/kg/day as cobalt chloride hexahydrate induced a significant 7% increase of body weight in Swiss mice, which is not considered biologically significant based on ATSDR's Guidance for the Preparation of Toxicological Profiles (cdc.gov)."*

COMMENT: Concentration, rather than dose would be preferred.

***RESPONSE**: This comment refers to the following sentence in section 2.4 (Respiratory): "However, at a similar dose of 0.0175 mg Co/m3 there were no effects observed in workers after a chronic occupational exposure for 3 years." The suggested edit was included and the sentence now reads: "However, at a similar concentration of 0.0175 mg Co/m3 there were no effects observed in workers after a chronic occupational exposure for 3 years."*

COMMENT: Specify if this is an increased incidence or severity

***RESPONSE**: This comment refers to the following sentence in section 2.4 (Respiratory): "The exposed workers also exhibited increased cough (11/91), wheezing (4/91) and upper airway irritation (40/91)." The phrase "increase incidence" was added to specify and the sentence now reads: "The exposed workers also exhibited increased incidence of cough (11/91), wheezing (4/91), and upper airway irritation (40/91)."*

COMMENT: The significance of retained lavage fluid is unclear consider adding the author's interpretation of this result.

***RESPONSE**: This comment refers to the following sentence in section 2.4 (Respiratory): "A 2-week exposure to cobalt chloride at 2.4 mg Co/m3 increased lung weight by 20% and retention of lavage fluid by 53% in female Hartley guinea pigs." The following sentence was added to clarify: "As per the authors, the significance of retained lavage fluid is unclear."*

COMMENT: Infection? or inflammation. If infection (which was not uncommon in animal studies conducted in this time period) – this is an important co-exposure/confounder.

***RESPONSE**: This comment refers to the following sentence in section 2.4 (Respiratory): "Male albino rats exposed to 9 mg Co/m3 for intermittently for 3 months showed lung infection, edema, congestion and bronchitis." The word "infection" was replaced with "inflammation" and the sentence now reads: "Male albino rats exposed to 9 mg Co/m3 intermittently for 3 months showed lung inflammation, edema, congestion, and bronchitis."*

COMMENT: Indicate specific outcome measures (e.g., organ weight, pathology). These will be less sensitive when compared with functional studies using EKG or echo methods.

***RESPONSE**: This comment refers to the following sentence in section 2.5 (Cardiovascular): "No signs of cardiovascular toxicity were observed in experimental studies where animals were exposed to concentrations ranging from 0.625 to 19 mg Co/m3 for intermediate and chronic durations in F344/N rats and 0.625 to 76 Co/m3 for intermediate and chronic durations in B63F1 mice." Results that are not biologically significant are not reported. No edits needed.*

COMMENT: Indicate whether the urine cobalt levels were elevated or in the normal range. As written it is unclear whether an occupational exposure occurred. Line 3 – indicate more clearly the transition to animal data.

RESPONSE*: This comment refers to the following sentence in section 2.7 (Hematological): "The workers used protective masks since 2002 which lowered the urinary cobalt levels." The sentence was edited for further clarity: "The workers used protective masks since 2002 which lowered the urinary cobalt levels compared to workers without protective gear."*

COMMENT: It is not clear that this represents an inhalation exposure per se versus dermal exposure to contaminated air.

RESPONSE*: This comment refers to the following sentence in section 2.11 (Dermal): "One study examined dermal effects in humans after occupational inhalation exposure to cobalt. Metal factory workers (n=71) exposed to air cobalt concentrations ranging from 0.0001 to 0.019 mg/m3 had high self-reported prevalence of dry skin (42%) and eczema (6-7%)." Wahlqvist et al. 2020 assessed dermal effects from inhalation of cobalt, but not respiratory effects of hard metal cobalt inhalation exposure. No edits needed.*

COMMENT: Was PaO2 measured? how was anoxia determined?

RESPONSE*: This comment refers to the following sentence in 2.15 (Neurological): "Acute-duration oral exposure to cobalt sulphate in both Wistar rats and Swiss-Webster mice at doses of 194 mg Co and 123 mg Co per kg bodyweight resulted in anoxic convulsions, decreased motor activity, and impairments in reflexes." Singh and Junnarkar does not detail how anoxia was determined. It states that animals showed anoxic convulsions. No edits needed.*

COMMENT: Increased expression of what?

RESPONSE*: This comment refers to the following sentence in 2.15 (Neurological): "Akinrinde et al. (2019) showed that exposure to cobalt chloride hexahydrate caused deficits in performance on a battery of neurobehavioral tests along with an increase in expression by 60% at 67.5 mg Co/kg/day in Wistar rats." The phrase "of AChE activity as compared to controls" was added and the sentence now reads: "Akinrinde et al. (2019) showed that exposure to cobalt chloride hexahydrate caused deficits in performance on a battery of neurobehavioral tests along with an increase in expression by 60% of AChE activity as compared to controls at 67.5 mg Co/kg/day in Wistar rats."*

COMMENT: Latency in what behavioral test. This lack of detail occurs in other parts of this paragraph.

RESPONSE*: This comment refers to the following sentence in 2.15 (Neurological): "In an intermediate-duration oral exposure study where Sprague-Dawley rats were exposed to 20 mg Co/kg/day as cobalt chloride for 80 days in water, there was increased latency during retention testing by 342%." Bourg and Nation 1985 describe the behavioral test as "retention testing" which is already stated. No edits needed.*

COMMENT: More clearly indicate that this relates to an orthopedic repair

RESPONSE*: This comment refers to the following sentence in 2.16 (Reproductive): "One study of cobalt exposure associated with intramedullary nailing in Egyptian men (n=60) found evidence of impaired sperm motility, decreased sperm concentration, and decreased sperm count." This sentence was deleted as studies pertaining to use of cobalt in prosthetics are not included as the profile includes exposure to cobalt through inhalation, oral, and dermal routes as specified in ATSDR's Guidance for the Preparation of Toxicological Profiles (cdc.gov).*

COMMENT: Has the EPA performed a cancer risk assessment that drew this conclusion? If so then cite otherwise consider changing this to: The Environmental Protection Agency has not classified cobalt for carcinogenicity.

RESPONSE*: This comment refers to the following sentence in 2.19 (Cancer): "The Environmental Protection Agency has not classified cobalt for carcinogenicity, indicating that there is inadequate information to determine its cancer potential." The suggested edit was included and the sentence now reads: "The Environmental Protection Agency has not classified cobalt for carcinogenicity."*

COMMENT: Is "stable" needed – it implies "unstable" cobalt compounds behave differently – or change to metabolically stable

RESPONSE*: This comment refers to the following sentence in 2.20 (Genotoxicity): "In contrast to the results seen in bacteria, stable cobalt compounds were generally found to be genotoxic or mutagenic in mammalian assay systems." The word "stable" was removed and the sentence now reads: "In contrast to the results seen in bacteria, cobalt compounds were generally found to be genotoxic or mutagenic in mammalian assay systems."*

COMMENT: Change to release of cobalt ions from its salts. The second sentence is confusing.

RESPONSE*: This comment refers to the following sentences in 2.21 (Mechanism of Action): "Soluble and insoluble forms of cobalt give rise to toxicity and carcinogenicity in animal models following cellular uptake of the metal and subsequent release of cobalt ions its salts. These ions cause an immediate cascade of downstream biological effects. The extracellular release of cobalt ions from water-soluble compounds is transported into the cells thorough the ion channels or via endocytosis of poorly soluble cobalt compounds." The word "from" was added and the second sentence was edited for clarity: "Soluble and insoluble forms of cobalt give rise to toxicity and carcinogenicity in animal models following cellular uptake of the metal and subsequent release of cobalt ions from its salts. These ions elicit a cascade of downstream biological effects. The extracellular release of cobalt ions from water-soluble compounds is transported into the cells thorough the ion channels or via endocytosis of poorly soluble cobalt compounds."*

COMMENT: These figures show modeled data- the legend should indicate the theoretical status of the figures

RESPONSE*: This comment refers to Figure 3-1 in section 3.1.1 (Absorption). Figure title updated to include "Modeled" to indicate theoretical status of the figure.*

COMMENT: Provide form of cobalt – applies. To other tables e.g. 3-6 and 3-7

RESPONSE*: This comment refers to Table 3-3 in section 3.1.4 (Excretion). The table was updated to include the form of cobalt. Table 3-6 and 3-7 used two different forms of cobalt and are listed in the table separately as cobalt chloride and tri cobalt tetra chloride.*

COMMENT: Change to: PBPK models are biologically based tissue dosimetry models.

RESPONSE*: This comment refers to the following sentence in section 3.1.5 (Physiologically Based Pharmacokinetic/Pharmacodynamic Models): "PBPK models are also called biologically based tissue dosimetry models." The phrase "also called" was removed and the sentence now reads: "PBPK models are biologically based tissue dosimetry models."*

COMMENT: Change to: The ICRP model has several underlying assumptions. Absorption of ingested cobalt is assumed to be 60% in infants up to 3 months of age, 30% from 3 months to 15 years of age, and 10% after age 15 years…

RESPONSE*: This comment refers to the following sentence in section 3.1.5 (Physiologically Based Pharmacokinetic/Pharmacodynamic Models): "Absorption of ingested cobalt is assumed to be 60% in infants up to 3 months of age, 30% from 3 months to 15 years of age, and 10% after age 15 years." The following sentence was revised as suggested: "The ICRP model specific to cobalt (ICRP 1995) has several underlying assumptions. Absorption of ingested cobalt is assumed to be 60% in infants up to 3 months of age, 30% from 3 months to 15 years of age, and 10% after age 15 years."*

COMMENT: Used how or by whom?

RESPONSE*: This comment refers to the following sentence in section 3.1.5 (Physiologically Based Pharmacokinetic/Pharmacodynamic Models): "The new human alimentary tract model (HATM) will be used together with the human respiratory tract model (HRTM; ICRP, 1994a,b)." The source was added and the sentence now reads: "The new human alimentary tract model (HATM) was used together with the human respiratory tract model in Unice et al. (2020) (HRTM; ICRP, 1994a,b)."*

COMMENT: Change to: Modeling of other chemical forms of cobalt, e.g., cobalt oxides, used the following assumptions…

RESPONSE*: This comment refers to the following sentence in section 3.1.5 (Physiologically Based Pharmacokinetic/Pharmacodynamic Models): "Other forms, e.g., cobalt oxides, used the following assumptions: slow absorption rates (ICRP 'Type S'), with a rapid fraction of 0.01, rapid dissolution half-life of 17 hours, slow dissolution half-life of 19 years, and absorption fraction from the alimentary tract of 0.001." The suggested edit was included and the sentence now reads: "Modeling of other chemical forms of cobalt, e.g., cobalt oxides, used the following assumptions: slow absorption rates (ICRP 'Type S'), with a rapid fraction of 0.01, rapid dissolution half-life of 17 hours, slow dissolution half-life of 19 years, and absorption fraction from the alimentary tract of 0.001."*

COMMENT: This statement appears to be at odds with previous statements regarding the PBPK models. The text on PBPK models should explicitly state whether the cited models were developed for animal and humans (e.g., the model assumptions may be based on animal data). Also, it's not clear whether this statement applies more broadly to inhalation studies versus "animal lung retention" studies.

RESPONSE*: This comment refers to the following sentence in section 3.1.6 (Animal-to-Human Extrapolations): "Retention and clearance of inhaled physiologically insoluble 57Co particles varies widely across species, illustrating the potential difficulty of extrapolating the results of animal lung retention experiments to humans even qualitatively." The sentence was edited for clarity and now reads: "Retention and clearance of physiologically insoluble 57Co particles varies widely across species, illustrating the potential difficulty of extrapolating the results of animal lung retention experiments to humans even qualitatively."*

COMMENT: There are competing processes here including age-related changes in deposition and translocation. It's not clear why translocation alone account for these differences.

RESPONSE*: This comment refers to the following sentence in section 3.2 (Children and Other Populations that are Unusually Susceptible): "The authors attributed this to a faster rate of translocation of cobalt from the lung to the blood, which could enhance subsequent excretion. The youngest animals had a significantly faster translocation rate." The study authors did not provide further clarifications on this aspect. The sentence now reads: "The authors attributed this to a faster rate of translocation of cobalt from the lung to the blood, which could enhance subsequent excretion. The youngest animals had a significantly faster translocation rate which was not further explained by the study authors."*

COMMENT: More details are needed – e.g., is this mucociliary clearance? Measured how (e.g., in vitro, in vivo, radiolabelled particles)?

RESPONSE*: This comment refers to the following sentence in section 3.2 (Children and Other Populations that are Unusually Susceptible): "There were no significant differences in mechanical clearance rates." Further detail was added for clarity and the sentence now reads: "There were no significant differences in mechanical clearance rates of 57Co labelled Co3O4 in animals of different ages."*

COMMENT: Earlier text suggested that the ICRP PBPK model could be applied to children.

RESPONSE*: This comment refers to the following sentence in section 3.2 (Children and Other Populations that are Unusually Susceptible): "Available PBPK models have been developed for adults and potentially could be modified by applying child specific parameters." This sentence has been deleted as this information has already been included in earlier text.*

COMMENT: Krachler used ICP-MS following digestion of samples – they did not speciate the cobalt per se so it is unknown whether the excreted cobalt was in an inorganic form.

RESPONSE*: This comment refers to the following sentence in section 3.2 (Children and Other Populations that are Unusually Susceptible): "Cobalt is detected in human breast milk at concentrations in the parts per billion (ppb) range in the inorganic form (Byczkowski et al. 1994; Krachler et al. 1998). Krachler et al. has been deleted from the citations.*

COMMENT: Why "stable" cobalt?

RESPONSE*: This comment refers to the following heading in section 3.2 (Children and Other Populations that are Unusually Susceptible): "Health Effects from Exposure to Stable Cobalt." The word "stable" has been removed and the heading now reads: "Health Effects from Exposure to Cobalt."*

COMMENT: Consider changing to: Since cobalt binds to plasma transferrin, which also binds iron, the potential exists for cobalt to affect iron transport or metabolism.

RESPONSE*: This comment refers to the following sentence in section 3.4 (Interactions with Other Chemicals): "Since cobalt binds to plasma transferrin, which also binds iron, the potential exists for cobalt to affect iron metabolism." The phrase "transport or" has been included and the sentence now reads: "Since cobalt binds to plasma transferrin, which also binds iron, the potential exists for cobalt to affect iron transport or metabolism."*

COMMENT: Which animal species? Exposure route? Outcomes?

RESPONSE*: This comment refers to the following sentence in section 3.4 (Interactions with Other Chemicals): "Hard metal dusts, consisting of 5–10% cobalt with the balance being tungsten carbide, was considerably more toxic than cobalt or tungsten carbide particles alone." Animal species, exposure route and outcomes are discussed in Chapter 2. No edits needed.*

COMMENT: The VIII designation is no longer used and should be deleted.

RESPONSE*: This comment refers to the following sentence in section 4.1 (Chemical Identity): "It is a member of Group 9 (VIII) of the periodic table along with rhenium, iridium, and meitnerium, and adjacent to iron and nickel. There is only one stable isotope of cobalt, 59Co." The VIII designation was removed and the sentence now reads: "It is a member of Group 9 of the periodic table along with rhenium, iridium, and meitnerium, and adjacent to iron and nickel. There is only one stable isotope of cobalt, 59Co."*

COMMENT: Incomplete sentence. Does not apply to all isotopes (e.g., 59Co)

RESPONSE*: This comment refers to the following sentence in section 4.1 (Chemical Identity): "All cobalt isotopes have half-life less than 24 hours." The sentence has been revised to say that cobalt isotopes have half-lives of varying lengths, but most are less than 24 hours: "Cobalt isotopes have half-lives that are specific to the isotope, and most are less than 24 hours (NNDC 2021)."*

COMMENT: Not clear what is meant by "behave the same in biological systems" since gamma emitters have different biological effects versus non-radioisotopic forms.

RESPONSE*: This comment refers to the following sentence in section 4.1 (Chemical Identity): "Isotopes are the same element, so they undergo the same chemical reactions and behave the same elicit similar health effects in biological systems." The sentence has been revised for clarity to read, "The isotopes of cobalt have the same chemical and physical properties, so they interact the same with biological systems."*

COMMENT: Curious – does this imply that human exhaled breath studies are evaluating particulate emission of cobalt? This may be worth mentioning earlier.

RESPONSE*: This comment refers to the following sentence in section 4.2 (Physical and Chemical Properties): "Cobalt is also an essential trace element found in Vitamin B-12. Cobalt and cobalt compounds are nonvolatile and are emitted to the atmosphere in particulate form." Chapter 3 Section 3.1 includes the following text "Goldoni et al (2004) measured cobalt in the exhaled breath of hard metal workers and found cobalt in the exhaled breath from 11.9 to 741 nanomoles/liter with levels higher at the end of the shift. Conversely, another study reported that exhaled breath concentrations of cobalt were not correlated to workplace air concentrations, which may limit its usefulness as a biomarker (Broding et al. 2009).". There are no additional studies that examine human exhaled breath studies evaluating particulate emission of cobalt. The current body of literature only examines emissions in the atmosphere. The following sentence was moved to the end of the paragraph: "Cobalt is also an essential trace element found in Vitamin B-12."*

COMMENT: Provide reference.

RESPONSE*: This comment refers to the following sentence in section 5.4.2 (Transformation and Degradation): "The rank order of species concentration in seawater was estimated to be: CoCO3>free Co+2>CoSO4≥CoHCO3+." The citation has been added to the end of the sentence and now reads as follows "The rank order of species concentration in seawater was estimated to be: CoCO3>free Co+2>CoSO4≥CoHCO3+ (Mantoura et al. 1978).".*

COMMENT: Move to the end of the previous sentence (Line 18).

RESPONSE*: This comment refers to the following sentence in section 5.4.2 (Transformation and Degradation): "Freshwater environments have comparable levels of vitamin B_{12}." The sentence has been moved to the end of the previous paragraph as suggested.*

COMMENT: Studies in cattle as well.

RESPONSE*: As per ATSDR's Guidance for the Preparation of Toxicological Profiles (cdc.gov), cattle studies are not included in the profile.*

COMMENT: Multiple reference citations are incomplete (missing journal, volume, page number etc).

RESPONSE*: Reviewed endnote library and filled in missing reference information as suggested.*

COMMENT: The authors should define stable cobalt (here and elsewhere) – suggest stating stable isotope (or similar). Stable can have multiple meanings.

RESPONSE*: The sentence has been edited for consistency. Text reads as follows "This section only discusses the MRLs for cobalt.". Statements related to radioactive cobalt are identified throughout the profile.*