COMMENTS ON ATSDR TOXICOLOGICAL PROFILE FOR COBALT

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Executive Summary

The Cobalt Institute requested that Stantec ChemRisk review the key findings of the Toxicological Profile for Cobalt, Draft for Public Comment, issued by the Agency for Toxic Substances and Disease Registry (ATSDR) in January of 2023. Based on this review, Stantec ChemRisk identified the following key issues recommended for consideration in the revision:

- Exclusion of important literature addressing respiratory toxicity, cancer, and genotoxicity and associated mode of action (Section 2.1.1)
- Concerns regarding the derivation of the minimum risk level (MRL) for inhalation and oral exposure; such concerns included:
    - Limitations in Nemery, et al. 1992, the study upon which ATSDR relied for the derivation of the chronic inhalation MRL
    - Limitations in the selection of the point of departure from Nemery, et al. 1992 and lack of consideration for weight of evidence
    - Selection of polycythemia as the key health effect for the derivation of the oral acute and intermediate MRL, particularly given the reversibility of this effect upon cessation of exposure

Given these concerns, we urge ATSDR to consider the points herein, including consideration of additional literature not identified by ATSDR, in the revision of the toxicological profile. Even if decisions regarding the selection of points of departure and derivation of the MRLs do not change and/or are driven by policy decisions within the agency, discussion of these points is important for contextualizing for consideration by risk managers when relying on agency-identified hazard dataset and/or screening values.

1 Introduction

The Cobalt Institute requested that Stantec ChemRisk review the key findings of the Toxicological Profile for Cobalt, Draft for Public Comment, issued by the Agency for Toxic Substances and Disease Registry (ATSDR) in January of 2023. As part of this review, we considered the primary conclusions regarding hazards associated with cobalt exposure, with a focus on inhalation pathways, and any changes in these findings and or basis of findings when compared to the most recent profile dated April 2004 (ATSDR, 2004). In addition, we considered the key studies and methods used for derivation of the minimum risk levels, as determined by ATSDR. The findings of these analyses are described in the sections below.

2 Review of Key Findings

2.1.1 REVIEW OF HAZARD CONCLUSIONS

The general hazard conclusions, as summarized by ATSDR in Section 1.2, are consistent with previous agency assessments for respiratory and hematologic effects and are consistent with the available literature on cobalt. Though effects on body weight were acknowledged in previous assessments, they were not noted as key effects observed associated with exposure to cobalt; it is unclear why the authors considered it essential to highlight this effect, particularly as these effects occur at higher doses than other observed effects and are not confirmed by available epidemiology studies. Contrastingly, the summary of key health effects for cobalt excludes consideration of other reported health effects, such as cardiac and immune responses. In particular, in the health effects review sections for both cardiovascular and immune response (e.g. Sections 2.5 and 2.14, respectively), ATSDR notes there are no available studies in humans evaluating either endpoint, in stark contrast to the 2004 assessment which includes studies that report cardiomyopathy and sensitization/occupational asthma related to cobalt exposures in humans, and more recently available literature addressing these endpoints (e.g. Linna, et al. 2020). Though the results of these studies may be confounded by other contributing factors, consideration of this available literature is important for contextualizing findings related to cobalt exposures, including acknowledgement of confounders.

In general, though conclusions regarding certain hazards are consistent with previous assessments and the available literature, ATSDR excluded or missed several important studies, particularly related to occupational exposures and disease outcomes, with no explanation as to why they were not considered relevant. Most notably, several studies evaluating pulmonary function outcomes were excluded, critical to the overall assessment as ATSDR bases the minimum risk level (MRL) on effects observed on pulmonary function from Nemery, et al. (1992). Secondly, though some of the references addressing cancer effects are cited elsewhere, the authors of this assessment did not include any consideration for human epidemiological studies evaluating cancer outcomes. As most regulatory agencies worldwide regulate cobalt based on carcinogenicity as a key health effect and ATSDR toxicological profiles are routinely relied upon to provide state-of-the-art toxicological summaries of chemicals, this omission is particularly egregious. Additional details on these exclusions are found below.

In addition to the aforementioned key studies on cancer and respiratory endpoints, ATSDR likely similarly missed many other studies evaluating cobalt toxicity, particularly in worker populations. We advise a reconsideration of the literature search methods to ensure inclusion of any other studies that would be warranted. For the purposes of this feedback, we focus on studies related to key health outcomes and/or for endpoints that drove decision-making regarding the MRL. However, other endpoints may suffer from similar deficiencies and, in fact, even a cursory review of the references suggests the absence of some potentially relevant literature on topics such as thyroid effects and cardiac effects.

2.1.1.1 Respiratory Toxicity

As summarized above, ATSDR failed to identify or excluded occupational exposure studies that reported on respiratory toxicity endpoints, including pulmonary function, respiratory symptoms, and occupational asthma (an immune response manifesting in pulmonary effects), including (but possibly not limited to):

- Al-Abcha, et al. 2021- a case-series on occupational asthma in workers with cobalt exposures;
- Andersson, et al. 2020- conducted dose response modeling on pulmonary function, markers of irritation, general respiratory symptoms and asthma in hard metal workers;
- Demedts, et al. 1984- a case series on respiratory effects in workers with cobalt exposures from diamond polishing
- Fischbein, et al. 1992- a case-series reporting on respiratory symptoms in hard metal workers;
- Gheysens, et al. 1985- a case series on respiratory effects and sensitization in workers with exposure to cobalt from diamond polishing
- Meyer-Bisch, et al. 1989- a cross-sectional study reporting on pulmonary function and respiratory symptoms in hard metal workers;
- Rehfisch, et al. 2012- a follow-up study on pulmonary function and respiratory symptoms in hard metal workers;
- Roto, 1980- an epidemiology study of workers in cobalt and zinc metallurgic industry; reports on asthma and other respiratory symptoms;
- Swennen, et al. 1993- a cross-sectional study evaluating workers in a cobalt refinery for health effects, including pulmonary function testing, reporting of respiratory symptoms, and biomarkers of cobalt exposure;
- Verougstraete, et al. 2004- a follow-up study of Swennen, et al. 1993;
- Walters, et al. 2014- a case-series on occupational asthma and sensitization to cobalt in workers in automotive valve manufacturing

Though some of these studies may have significant limitations related to study design, type, or availability of cobalt exposure data, they all could contribute to the discussion regarding the impacts of cobalt on respiratory effects. Some studies may even be appropriate in an evidence integration approach (see Section 2.1.2.3) related to derivation of a minimum risk level (MRL) for inhalation.

2.1.1.2 Cancer

As noted previously, the recent draft toxicological profile for cobalt published by ATSDR excluded important epidemiology studies of occupational cohorts reporting on cancer effects in humans. Notably, the previous ATSDR profile on cobalt from 2004 included reference to and discussion of several important studies on human occupational exposure to cobalt that have been omitted from the current profile for reasons that are not clear. These studies include: Mur et al., 1987; Moulin et al., 1993; Lasfargues et al., 1994; Moulin et al., 1998; Moulin et al., 2000; and Wild et al., 2000. The current ATSDR draft toxicological profile for cobalt states “no studies were identified that reported significant cancerous effects in humans following inhalation, oral, or dermal exposure to cobalt.” However, a discussion of the studies that exist but are generally negative for cancer outcomes is critical for summarizing existing toxicity information. As the ATSDR toxicological profile is a frequently relied upon resource for the summary of important studies on health effects of chemicals, those excluded studies are essential for inclusion to provide evidence regarding effects of cobalt in humans. In addition to the studies excluded from the previous assessment, the authors of the current profile did not identify more recently published literature addressing cancer in humans from epidemiology studies, including: Holy et al., 2022; Zhang et al., 2021; Marsh et al., 2009; Pavilonis et al., 2017; Svartengren et al., 2017; and Tüchsen et al., 1996. Notably, some of these studies are included in the profile to provide evidence regarding other health effects potentially associated with cobalt exposure; any rationale for their exclusion as it relates to evaluating cancer is unclear and/or not provided. Altogether, the weight of evidence indicates that human occupational exposure to cobalt is unlikely to result in an elevated cancer risk, a conclusion that is supported by a recent meta-analysis on the topic (Holy et al., 2022). It is crucial that ATSDR includes such a review to facilitate an understanding of the available epidemiology literature on cancer with exposure to cobalt.

2.1.1.3 Genotoxicity and Mode of Action

In addition to the egregious exclusions of important studies, ATSDR misrepresented key studies related to genotoxicity that are important for weight of evidence conclusions regarding mode of action associated with cobalt carcinogenicity. Kirkland, et al. (2015) a comprehensive study of *in vitro* and *in vivo* mutagenicity and clastogenicity for a variety of soluble and insoluble cobalt compounds, is not discussed in any level of detail; only cursory conclusions are provided in Tables 2-7 and 2-8. No differentiation of conclusion are made by cobalt compound, though the authors make observations regarding soluble and insoluble forms of cobalt, noting that insoluble forms of cobalt are not genotoxic in any assay tested, whereas soluble forms of cobalt display some evidence of genotoxicity *in vitro* (but not *in vivo*), effects the authors indicate are related to oxidative stress rather than direct interaction with DNA. In fact, for most of the studies described in this section, there is no indication of the form of cobalt, which is important for understanding genotoxicity potential as these effects are thought to be mediated through the solubilization of the Co^{+2} ion, as summarized by ATSDR in Section 2.21. Furthermore, the information regarding the results of Kirkland, et al. (2015), are misrepresented in Table 2-7, where it is indicated that *in vivo* exposures to cobalt compounds caused increases in clastogenicity and chromosomal aberration. This reporting is in contrast to both 1) the only text description of this study included in the profile ("Oral exposure to cobalt compounds studied by Kirkland et al. (2015) did not elicit any chromosomal aberrations in the bone marrow or sperm" and 2) the description of the *in vivo* findings provided by the study authors ("No biologically relevant induction of MN or CA has been found in bone marrow of rodents treated with cobalt sulphate, cobalt monoxide, tricobalt tetraoxide, cobalt resinate or cobalt acetyl acetonate in the present studies").

In addition to mischaracterization and/or misrepresentation of some of the genotoxicity assays that are reviewed in this profile, when discussing the mode of action, the authors do not differentiate mutagenicity from other forms of genotoxicity that may be mediated by factors such as oxidative stress. As reviewed by others, mutagenicity assays with cobalt compounds are generally negative. Furthermore, this profile provides reference to only a limited number of studies, excluding many that could have been considered in the overall weight of evidence regarding mutagenicity (including but not necessarily limited to: Wong (1988), Mochizuki and Kada (1982), Kada and Kanematsu, 1978; Rossman, et al. 1984, Nishioka (1975); Prazmo, et al. 1975; Amacher and Paillet, 1980). In addition, recent mode of action analyses were not considered, including: Burzlaff, et al. (2022); Derr, et al. (2022); van den Brule, et al. (2022); Verougstraete, et al. (2022); and Viegas, et al. (2022).

2.1.2 REVIEW OF MRL DETERMINATIONS

2.1.2.1 Chronic Inhalation MRL

The Derivation of the Minimal Risk Level (MRL) for chronic exposure by the inhalation route is provided in Appendix A (page A-8 to A-14). From the Appendix A, ATSDR stated, "A chronic-duration inhalation provisional MRL of 0.0001 mg/m3 (0.1 μg/m3) was derived for cobalt based on reduced respiratory spirometry parameter values in workers exposed chronically to cobalt in air (Nemery, et al. 1992). The MRL is based on a NOAEL of 0.0053 mg/m3 which was adjusted for intermittent exposure to a continuous exposure concentration of 0.0013 mg/m^3 and divided by a total uncertainty factor of 10 (10 for human variability)."

Overall, the derivation of the chronic inhalation MRL appears to based on the most sensitive toxicological endpoint. As described in the summary of health effects sections of the document, other effects demonstrated from available inhalation studies in humans or laboratory animals occur at significantly higher concentrations (often more of an order of magnitude) or have limited documentation that precludes quantitative concentration response assessment. Systemic effects are also observed following oral dosing – and thus are plausible endpoints for consideration. However, even the most sensitive of these systemic effects occur are relatively higher doses compared to respiratory tract effects. The most sensitive systemic effect (hematological effects) had a selected point of departure (POD) for the oral route of 68.1 mg/day. An approximate route extrapolation from the oral POD dose to an inhalation equivalent is

3 mg/m^3 (68.1 mg/day divided by breathing volume of 20 m^3 inhalation/day and assuming high systemic bioavailability of up to 100%). Thus, the potential POD for systemic effects is likely orders of magnitude above the inhalation POD for direct respiratory tract effects.

While the selection of respiratory tract effects is supported by the health effects data, the selection of the critical study and POD that were used for the MRL derivation should be revisited. If the approach presented in the External Review Draft is maintained based on policy choices, the implications of the resulting choices relative to a more scientifically-robust derivation should be described in much greater detail for transparency to risk managers. The comments below address three primary points:

1) There are many limitations in the design and documentation of the Nemery et al (1992) study that preclude its use as the sole and primary basis of the MRL. There are other studies that could be considered in a more comprehensive derivation.

2) The reliance on the No-observed adverse effect concentration (NOAEC) reported from Nemery, et al. (1992) should be reconsidered as the primary point of departure (POD) from the MRL derivation.

3) Since each of the studies upon which an MRL could be derived has some limitations, a more robust derivation can be derived using an evidence integration approach.

2.1.2.1.1 Reliance on Nemery, et al. 1992 as the critical study

The MRL derivation Appendix states that "[t]he Nemery, et al. (1992) study tested the lowest concentrations among all human and animal studies and demonstrated a dose-response relationship between reduced spirometry parameter values and cobalt exposure. Therefore, Nemery, et al. (1992) was selected as the critical study because it identified the lowest NOAEL for chronic-duration inhalation exposure and a corresponding LOAEL." While this might be the most conservative option among studies, it is not the most scientifically robust. There are other studies that had similar types of limitations that were not considered for the derivation. Thus, it appears that Nemery, et al. (1992) was selected solely on the basis of yielding the lowest POD, rather than on any other advantages it may offer in terms of study quality or reliability when compared to other considered studies. The limitations in Nemery, et al. (1992) = are significant and call into question the primary conclusions reached by ATSDR in using the study for MRL derivation. These key limitations included:

- Use of a cross-sectional study design. This type of study limits any evaluation or assertion of a causal relationship between exposure and outcome. None of the analyses accounted for other exposures that may affect lung function and many of the analyses did not control for known characteristics that affect lung function (age, height, sex, smoking status). Notably, the comparisons of continuous measures of lung function indices did not account for differences in age and smoking status between exposure groups.

- Incomplete exposure assessment potentially leading to exposure misclassification. This exposed group was dichotomized into a lower and a higher exposure group (mean ± standard deviation of personal air samples: 5.3 ± 3.2 µg/m3 and 15.1 ± 11.7 µg/m3, respectively). Air sampling was not conducted in every workshop and was in some cases estimated from area sampling or assumptions based on data from adjoining workshops.

- Study design and analysis considerations and transparency. Outcome measures of interest were FEV1, FVC, FEV1/FVC, and survey assessed upper airway irritation, cough, phlegm, dyspnea, and wheezing. Although lung function was measured in all cobalt exposed and non-exposed workers, respiratory symptoms were not collected in the control group without air sampling measures, and it is unclear whether urinary cobalt or smoking status were assessed in this group. Lung function measures in the highest exposure group appeared to be more decreased (compared to controls) in females than in males, but there were no statistically significant differences between exposure groups in FEV1 (% predicted) or FVC (% predicted) when results were stratified by sex. There were statistically significant differences between the low and high exposure groups for continuous measures of FEV1 and FVC, but not FEV1/FVC, adjusted by sex. These findings suggest restrictive lung disease; however, the comparisons did not adjust for age or smoking status. In the only analysis that examined lung function in non-smokers only, there were no differences in FEV1 (% predicted) or FVC (% predicted) by cobalt exposure group. Self-reported upper airway irritation was significantly more prevalent in the highest exposure group. However, although this finding was stated to not be associated with sex or smoking status, the data were not shown. Cough was statistically significantly more prevalent in the highest exposure group, but the authors stated that cough was more frequently reported in women and in current smokers (data not provided).

Some of these limitations are noted by ATSDR, which is appreciated in providing for transparency in the MRL derivation process.

2.1.2.1.2 Selection of the POD from Nemery, et al. 1992

Despite the limitations in the study, the MRL was derived selecting the exposure estimate for the low-exposure group of 0.0053 mg/m^3 as the POD for MRL derivation. A benchmark dose modeling (BMD) approach was also considered that appeared to have been conducted in a manner consistent with current methods. ATSDR noted stated that: “Among the remaining models for both FVC and FEV1 data, the Linear model for FEV1 data had the lower AIC. Thus, the BMDL of 0.018 mg Co/m^3 was considered as the POD. It is higher than the study NOAEL and LOAEL of 0.0053 and 0.0151 mg Co/m^3, respectively, and would subsequently result in a higher MRL than one derived using the study NOAEL. Accordingly, the BMDL was not chosen as the POD. The NOAEL was chosen as the POD. Using the NOAEL is more protective of human health and supported by the fact that there is uncertainty in the exposure duration due to lack of information in the Nemery et al (1992) study.” This final selection of the POD was apparently based on a policy choice, not based on the statistical characteristics of the available dose-response. Further scientific justification of the choice to default to the NOAEL in lieu of relying upon the BMDL should be considered and included in the profile. The observation that the BMDL was above the reported LOAEL is not sufficient rationale for selecting the NOAEL, as this observation reflects the nature of the data – limited dose response, limited degree of change in response magnitude, and significant variability possibly attributable to other factors (like smoking). In fact, the BMDL in the range of high exposure group concentration is concordant with the study result that showed no difference in FEV1 of FVC1 among non-smokers by cobalt exposure group (Nemery, et al. 1992).

ATSDR in Appendix A noted several key limitations that might affect interpretation of the Nemery, et al. (1992): “The study assumed that all workers were chronically exposed to cobalt, but the length of employment was not stated and the workplace exposure concentrations prior to air sampling were unknown. The study authors also stated there was uncertainty in the methodology used to sample air, stating that exposure could have been underestimated. For this reason, the lower concentration between the NOAEL and BMDL was chosen as it is a more protective. Additionally, there were more smokers in the low and high dose exposure groups compared to the control group.” While these limitations are important, they are reasons to reduce reliance on Nemery, et al. (1992) as the qualitative basis for the MRL, not a reason to select the NOAEL over the BMDL from this study. To this point:

- These limitations of the study are significant and should be reflected in the ultimate derivation. Regarding duration not being “chronic”, this limitation could be addressed by electing a chronic rodent study as primary basis for the MRL, or through a duration adjustment of the POD. Simply selecting a conservative NOAEL is not directly addressing the specific uncertainty under consideration.
- If exposure was “underestimated” based on the sampling method, the actual cohort exposure would have been higher, and thus the NOAEL, LOAEL, and BMDL would be higher. Thus, using the NOAEL as reported recognizes it is may be a lower-than-needed estimate of the threshold for the effect.
- The lack of smoking status is a significant limitation, but again this could inflate the attribution of effects to Co and thus make the NOAEL and LOAEL conservative. ATSDR noted, “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 the highest treatment group. 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. Therefore, it is possible that smoking is causing an increase in cough in the 12% of individuals in the higher concentration exposure group.”

All these limitations suggest that the Nemery, et al. (1992) data are reporting an effect level that is lower the actual threshold for effects.

2.1.2.1.3 Use of Evidence Integration for MRL Determination

When considering these limitations in Nemery, et al. (1992), it is not surprising that the threshold identified from the study, as interpreted by ATSDR for the MRL derivation, appears much lower than and is not aligned with other equally robust inhalation data. ATSDR might consider an evidence integration approach that better weighs the limitations of various lines of evidence. It appears from the key inhalation data summarized by ATSDR in the MRL derivations section that one could consider three primary sources of data. Each of which – with a few considerations are noted below.

- In total, the body of evidence supports a derivation higher than that derived from the assigned NOAEL from Nemery, et al. (1992). At a minimum, further description of these options would help inform risk managers of the impact of policy-based decisions reflected in the currently proposed MRL for chronic exposure via the inhalation route.

- The BMD analyses of data from Nemery et al., (1992) suggest an onset of differences relative to controls of approximately of 0.018 mg/m^3 (the BMDL). The observed lower bound (the NOAEL of 0.0053 mg/m^3) should be and is below this BMDL.

- For Sauni et al (2010), ATSDR reported a NOAEL range of 0.03 to 0.15 mg/m^3. The lower bound from this study is generally in line with the BMDL from Nemery, et al. (1992). The NOAELs in Sauni, et al. might also be conservative, as co-exposure to other respiratory irritants were present; in fact, once exposures to irritant gases were eliminated through process change, the effects on pulmonary function in cobalt-exposed workers were no longer observed. The presence of confounding exposures was considered a major limitation in the ATSDR analyses that limited the use of this study – but also note that the impact of this co-exposure would have been to make the use of the data conservative (actual NOAEL higher than the reported NOAEL). In addition, this study contained data in workers without exposure to irritant gases (but with cobalt exposures) that could have been considered in the dose response assessment and/or a weight of evidence evaluation around effect levels.

- Other organizations have relied on the long-term inhalation studies in rodents at the primary basis for inhalation limits. In reviewing the data as summarized by ATSDR in the Appendix A – the combination of the data from a rat inhalation study seems to show a clear pattern of a NOAEL of 0.06 mg/m^3, with a LOAEL of 0.21 mg/m^3. Even a simple adjustment of the rat NOAEL for exposure duration relevant to the occupational scenario yields a worker scenario NOAEL of 0.012 mg/m^3 and LOAEL of 0.042 mg/m^3. [Note: this estimate adjusts the rat exposure values as follows: 0.06 mg/m^3 x 6 hrs/8hrs (exposure duration) x 6.7 m^3/10m^3 (resting vs light work breathing volume) / 2.5 (toxicodynamic uncertainty factor)].

This worker scenario equivalent values align well with other predicted thresholds from the examples above. The Nemery et al (1992) BMDL is consistent with both the NOAEL range from Sauni, et al. (2010) and the worker scenario derived POD range from the rat inhalation studies. Together, the three lines of evidence do not support using the selected NOAEL of 0.0053 mg/m^3 from Nemery, et al. (1992) as the primary basis for the MRL. Alternately, an evidence integration method considering all three of these lines of evidence would offer a more comprehensive approach to identifying the POD, whilst still remaining appropriately conservative.

In addition to the resources identified by ATSDR and summarized herein, there may be additional studies that could contribute to the overall evidence regarding the dose response associated with pulmonary effects from cobalt exposure. As noted in Section 2.1.1.1 of this report, ATSDR excluded several studies that reported on pulmonary effects in cobalt-exposed workers; these studies should also be evaluated for consideration in the weight of evidence and evidence integration to determine an appropriate MRL.

2.1.2.2 Acute and Intermediate Oral MRLs

Both the acute and intermediate oral MRLs are based on the development of polycythemia following oral cobalt exposure; these MRLs rely on the same study (Davis and Fields, 1958) and arrive at the same recommendation (an MRL of 0.03 mg/kg/d), in spite of being based on slightly different subsets of the individuals evaluated in that reference. Hematological effects have been observed in several studies evaluating the effects of oral exposure to cobalt, including in both animals and humans (Domingo, et al. 1984, Krasovski and Fridland, 1975, Sullivan, et al. 1969, Alexander, 1972, Davis and Fields, 1958, Duckham and Lee, 1976, Taylor, et al. 1977, Kesteloot, et al. 1968, Shrivastava, et al. 2010, Morin, et al. 1971). In some studies in humans, polycythemia is not observed with oral exposure to cobalt (Jaimet and Thode, 1955; Holly, et al. 1955); these studies may provide additional insight to no-effect levels for polycythemia. Notably, Jaimet and Thode, 1955 was not identified or cited by ATSDR in their review. Furthermore, Co has been used as a treatment for anemia and is also taken by athletes as a supplement to increase the oxygen-loading capacity of the blood (Thomas, 1956; Kriss et al., 1955; Voyce,1963; Lippi et al., 2006; Jelkmann and Lundby, 2011). Therefore, in some instances, the hematological effects against which the MRL is intended to protect are a desired outcome of cobalt exposure. While polycythemia may be considered adverse under chronic conditions (as a precursor to more serious effects, such as stroke), it is reversible upon cessation of cobalt exposure, as demonstrated in Davis and Fields, 1958, the study upon which ATSDR relied for derivation of the MRL. ATSDR does not discuss reversibility (particularly as it relates to adversity) of this effect when considering this endpoint as the point of departure for determination of an acute and/or intermediate MRL. We recommend that ATSDR discuss this point, particularly as this point is crucial for the exposure scenarios for non-chronic exposure scenarios (as consistent with the proposed MRLs). In addition, it may be useful to put this effect into context with other identified adverse effects from oral cobalt exposure, in order to contextualize the level of conservatism this may introduce to determination of the MRL.

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