

# Comments on the Hazard Identification Materials for Consideration in Listing Nickel and Nickel Compounds as Reproductive Toxicants Under Proposition 65

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# Executive Summary

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The California Office of Environmental Health Hazard Assessment (CalOEHHA) selected nickel and nickel compounds for consideration on the Proposition 65 list of chemicals that cause reproductive toxicity. As part of this process, CalOEHHA (2018) provided a review of the available human and experimental animal studies evaluating associations between nickel exposure and reproductive and developmental health outcomes to the Developmental and Reproductive Toxicant Identification Committee (DARTIC), and the committee is expected to render an opinion regarding whether nickel and nickel compounds have been clearly shown to cause reproductive toxicity at a meeting on October 11, 2018.

Based on the CalOEHHA (2018) evidence review, as well as a separate risk-of-bias analysis and evaluation of the results of the same studies reviewed by CalOEHHA, we conclude the following:

- While CalOEHHA conducted a substantial literature review, it did not use a systematic approach to assess the evidence. Study inclusion and exclusion criteria were not explicitly stated, study quality was not assessed in a consistent manner, and the evidence integration sections focused only on positive study results, without any consideration of study quality or relevance. This resulted in an evaluation that did not fully represent the state of the science regarding the potential reproductive and developmental toxicity of nickel and nickel compounds.
- Due to the lack of a systematic approach and evaluation of study quality, reliance on the CalOEHHA evidence review will limit the ability of DARTIC to form scientifically defensible opinions regarding the reproductive hazard potential of nickel, making it difficult for DARTIC to determine whether nickel and nickel compounds meet the CalOEHHA criteria for listing as a known reproductive toxicant.
- To address this issue, we conducted a risk-of-bias analysis of the epidemiology studies reviewed by CalOEHHA, using the National Toxicology Program (NTP) Office of Health Assessment and Translation (OHAT) Risk of Bias Rating Tool. The "risk of bias" of a study is the extent to which the results are credible for any reported link between exposure and outcome, based on the design and conduct of the study. In addition, we evaluated the results of the studies, with consideration of how the factors that can affect the risk of bias and study quality may have impacted the interpretation of the results. We also integrated evidence across studies, placing more weight on higher quality studies with lower risks of bias.
- Our risk-of-bias analysis found that all studies have an overall moderate risk of bias, indicating generally low quality, due to the lack of appropriate statistical approaches to assess potential confounding, the use of area-level exposure measurements, and an inability to assess the temporal relationship between nickel exposure and the outcome of interest.
- The epidemiology studies also do not allow for an evaluation of any specific form of nickel. Oxidic and water-soluble nickel are the predominant forms of nickel found in the studies of ambient air exposure and welders, while refinery workers are exposed to mixtures of nickel metal and soluble and insoluble nickel compounds.
- An evaluation of the results of the epidemiology studies, with consideration of how the factors that affect the risk of bias impact the interpretation of the results, indicates that the studies do not provide evidence that nickel and/or nickel compounds are male or female reproductive or developmental toxicants. Results across the various reproductive and developmental outcomes examined were

largely inconsistent or null, with no clear evidence for associations between nickel and any particular outcome.

- Of the three studies that investigated female reproductive effects, two reported null associations. The third study reported associations for a subset of the parameters tested; these results could be attributable to bias or confounders and have not been confirmed in other studies. The overall evidence from human studies does not support a causal association between nickel exposure and female reproductive effects.
- Of the eight studies that evaluated potential associations between nickel exposure and male reproductive outcomes, none accounted for important confounding variables, employed appropriate statistical approaches, or were able to assess temporal relationships because of their cross-sectional design. More importantly, because all the studies were found to have a moderate risk of bias, the validity of their results is questionable. Overall, the results for each of the male reproductive outcomes examined were inconsistent across studies, and do not support a hazard listing for nickel and/or nickel compounds as male reproductive toxicants.
- Twenty-eight studies evaluating potential associations between nickel exposure and various developmental outcomes, including birth defects, low birth weight, adverse pregnancy outcomes, autism spectrum disorder (ASD), early-life cancers, and DNA damage, were reviewed by CalOEHHA.
  - Seven studies evaluated nickel associations with birth defects. Two studies reported statistically significant associations with birth defects, whereas four reported no associations and one reported a statistically significant negative (*i.e.*, protective) association with nickel exposure. One of the positive studies was a nickel refinery study for which subsequent, more thorough investigations of the same cohort did not reproduce the positive findings. Because the majority of the studies reported null or negative results (including those with more reliable results as indicated by the risk-of-bias analysis), they do not support a causal association between nickel exposure and birth defects.
  - Ten studies evaluated nickel associations with measures of low birth weight. Four of these studies reported statistically significant, positive associations between nickel exposure and lower birth weight, one study reported a borderline statistically significant association, four studies reported no associations, and one study reported a negative (*i.e.*, protective) association. The study reporting a negative association had higher exposures and adequate statistical power to detect the effects on low birth weight reported in one of the positive studies, undermining the results of the latter study. Together, the studies of nickel and low birth weight do not provide evidence to support a causal association.
  - Additional studies examining nickel exposure and ASD, early-life cancers, pneumonias, spontaneous abortion and premature birth, and DNA oxidative damage do not provide evidence for a causal association, as each outcome was evaluated in only a single or few studies and none of the studies accounted for confounders.
- Based on our evaluation of the risk of bias and study results, we conclude that the epidemiology studies are of generally low quality, and do not provide evidence that nickel and nickel compounds present a reproductive or developmental hazard.

# 1 Introduction

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The California Office of Environmental Health Hazard Assessment (CalOEHHA) selected nickel and nickel compounds for consideration on the Proposition 65 list of chemicals that cause reproductive toxicity (which includes both reproductive and developmental toxicity). As part of this process, CalOEHHA provided hazard identification materials to the Developmental and Reproductive Toxicant Identification Committee (DARTIC), and the committee is expected to render an opinion regarding whether nickel and nickel compounds have been clearly shown to cause reproductive toxicity at a meeting on October 11, 2018. Included in these materials is a document CalOEHHA (2018) developed entitled *Evidence on the Developmental and Reproductive Toxicity of Nickel and Nickel Compounds*. This document reviews the available human and experimental animal studies evaluating associations between nickel exposure and developmental and reproductive health outcomes.

The CalOEHHA document summarizes each study in narrative form, but does not follow a systematic approach for evaluating study quality that is applied consistently across studies and that is considered during the integration of the evidence. We conducted a risk-of-bias analysis of the epidemiology studies reviewed in the CalOEHHA document, based on study quality characteristics that may have impacted the validity of the findings. In addition, we evaluated the results of the studies, with consideration of how the factors that can affect the risk of bias and study quality may have impacted the interpretation of the results. We also integrated evidence across studies, placing more weight on higher quality studies with lower risks of bias, and we considered the form of nickel to which the studied populations were likely exposed.

Based on our evaluation of the risk of bias and study results, we conclude that the epidemiology studies are of generally low quality, and do not provide evidence that nickel or nickel compounds present a reproductive or developmental hazard. The bases for these conclusions are described in the following sections.

## 2 Systematic Review

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### 2.1 CalOEHHA Evidence Review

In its review of the evidence for hazard identification for nickel and nickel compounds, CalOEHHA (2018) summarized the available epidemiology and experimental animal studies evaluating associations between nickel exposure and developmental and reproductive health outcomes.

The literature search strategy to identify relevant studies was provided in an appendix and includes a list of the databases and search terms that were used, but there is no discussion of the decision criteria used for study inclusion or exclusion. The document also does not discuss the number of studies identified in the literature searches nor the steps taken to narrow down the initial list of studies to those selected for review.

The study summaries provided by CalOEHHA (2018) are in narrative form, with tables of basic study characteristics provided in an appendix. The study narratives do not follow any consistent format, with certain study limitations that were noted by the study authors or identified by CalOEHHA provided in a comments section at the end of some, but not all, of the narratives. Similarly, the study tables in the appendix provide some information on study limitations in a "Comments" column, but neither the narratives nor the tables evaluate study quality in a manner that is consistent across all studies.

For each of the three health outcomes assessed (developmental toxicity, female reproductive toxicity, and male reproductive toxicity), CalOEHHA (2018) conducted what it referred to as an "integrative" evaluation of the human and animal evidence, both separately and together. For the integrative evaluations of each realm of evidence alone, studies were grouped by similar specific outcomes (*e.g.* fetal growth, congenital malformations, autism spectrum disorders) for tabulation of the nickel exposure levels and study results, with no discussion of study quality. The integration of human and experimental animal evidence together focuses only on the positive results of studies for specific outcomes, and does not consider study quality or null results. There is also no comparison of the reported effect levels between experimental animals and humans or the exposure levels between the general population and occupationally-exposed workers.

CalOEHHA (2018) did not use a systematic approach to summarize the evidence for hazard identification, resulting in an evaluation that, even if comprehensive, lacks transparency and reproducibility and does not fully represent the state of the science regarding the potential reproductive and developmental toxicity of nickel compounds. As discussed below, the current evidence review does not provide a sound basis for rendering opinions regarding the potential reproductive and developmental hazards of nickel and nickel compounds.

### 2.2 DARTIC Review

The DARTIC is considering the review of the evidence by CalOEHHA (2018) to render an opinion regarding whether nickel and nickel compounds have been clearly shown to cause reproductive toxicity. To guide its decision, DARTIC is relying on a set of criteria for recommending chemicals for listing as "known to the State to cause reproductive toxicity" (CalOEHHA, 1993). The criteria document states that to be recommended for listing, there must be either sufficient evidence for developmental and reproductive

effects in humans, limited or suggestive evidence in humans supported by sufficient experimental animal data, or sufficient evidence in experimental animals such that extrapolation to humans is appropriate.

"Sufficient" evidence in humans is defined as convincing evidence to support a causal relationship from any of a variety of epidemiological studies "so long as the study or studies are valid according to generally accepted principles" and the studies include "accurate exposure and toxicity endpoint classification and proper control of confounding factors, bias, and effect modifiers" (CalOEHHA, 1993). The "weight-of-evidence" considerations for sufficient evidence state that effects should occur in more than one human study if the listing will be based on epidemiologic evidence alone, but that data from a single, well-conducted study showing a clear relationship between exposure and effect may be sufficient for listing if there are no equally well-conducted studies that do not show an effect and that "have sufficient power to call into question the repeatability of the observation in the positive study" (CalOEHHA, 1993).

The criteria document does not define "limited" or "suggestive" evidence in humans, so it is unclear how DARTIC is supposed to consider these criteria. Even so, the manner in which CalOEHHA (2018) summarized the available literature for nickel compounds will likely make it difficult for DARTIC to apply the CalOEHHA criteria for listing (CalOEHHA, 1993). This is because the study narratives and tables of results do not allow for an evaluation of whether the epidemiology studies are scientifically valid, with accurate exposure and outcome classification and proper control of confounding factors and bias; nor do they allow for an evaluation of whether there is convincing evidence to support a causal relationship between exposure to nickel and nickel compounds and developmental or reproductive effects. Ideally, the review of the evidence should have been conducted in a consistent and reproducible way, incorporating study quality considerations into the evidence integration process, to assist DARTIC in forming scientifically defensible opinions.

### 2.3 Systematic Review Approaches

Many scientific and regulatory agencies are incorporating systematic review approaches in their evaluations of chemical hazard and risk to minimize subjectivity and increase the transparency, rigor, and consistency of their reviews. These include the United States Environmental Protection Agency (US EPA, 2018a,b), the European Food Safety Authority (EFSA, 2017), the Texas Commission on Environmental Quality (TCEQ, 2017), and the National Toxicology Program (NTP, 2015a). In contrast, CalOEHHA did not incorporate the principles of systematic review (particularly the best practices for study selection, study quality evaluation, and evidence integration) in its evidence review.

As noted above, CalOEHHA (2018) did not provide clear methods or decision criteria for inclusion or exclusion of human and experimental animal studies in its evidence review for nickel compounds. This is not consistent with the principles of transparency fundamental to systematic reviews. By not including clear study inclusion and exclusion criteria and justification for study exclusion, it is unclear whether all relevant studies were included for review by CalOEHHA and what the decisions for excluding studies were based upon. Thus, it is unclear whether all pertinent information regarding the potential reproductive and developmental toxicity of nickel compounds is available in the evidence review for consideration by DARTIC.

CalOEHHA (2018) also did not assess study quality in a consistent manner across studies in its evidence review of nickel compounds. Because CalOEHHA did not use a systematic approach to evaluate study quality prior to evaluating study results, with the application of the same set of predefined study quality criteria across all studies of the same realm (epidemiology or experimental animal), each study could not be evaluated in an objective manner so that all study results could be considered and given appropriate weight based on study quality rather than whether the findings were positive or null.

Another issue is that the evidence integration sections in the CalOEHHA (2018) evidence review of nickel compounds focused on positive study results, without any consideration of study quality or relevance. In adherence with systematic review principles, evidence reviews should include a discussion regarding how the factors that affect study quality impact the interpretation of the results, how results from low quality studies will be considered (particularly if they are inconsistent with results from higher quality studies), and how null and negative study findings will be integrated into the evaluation to inform the interpretation of positive findings. This decreases potential bias in how each of the findings is used to draw conclusions regarding the strength of the evidence. CalOEHHA (2018) did not provide such a discussion, and it does not appear that study quality was sufficiently considered by CalOEHHA when integrating the results of epidemiology studies.

Evidence from human and experimental animal studies should be integrated in a manner that allows each study type to inform the interpretation of the other. This should consider questions of human relevance, including information on human-relevant exposures, dose-dependent effects, and species-specific differences in toxicokinetics or susceptibility. This allows for sound judgment to be used when evaluating whether study findings should constitute evidence for or against the hazard question. CalOEHHA (2018) focused only on the positive results of studies in humans and experimental animals separately, and did not compare the reported effect levels between species in its integration of the evidence.

## 3 Epidemiology Study Quality and Results

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CalOEHHA (2018) identified 40 epidemiology studies in its evidence review for nickel and nickel compounds; three studies evaluated female reproductive outcomes, nine studies evaluated male reproductive outcomes, and 28 studies evaluated developmental outcomes. Study characteristics and results for each of these studies are summarized here in Tables 1 and 2, respectively. It is notable that one male reproductive study (Slivkova *et al.* 2009) and one developmental study (Huang *et al.*, 2011) identified by CalOEHHA did not actually evaluate statistical associations between nickel exposure and any health outcome and should not be included in a hazard assessment of the potential reproductive toxicity of nickel compounds.

Below, we consider the different forms of nickel to which the populations in the identified epidemiology studies may be exposed. Then, because no specific criteria were used by CalOEHHA (2018) to evaluate the quality of the identified studies, we conducted a standardized risk-of-bias analysis based on epidemiology study quality characteristics that may have impacted the validity of the study findings. We also evaluated the results of the studies, with consideration of the form of nickel evaluated and how the factors that affect the risk of bias impact the interpretation of the results.

### 3.1 Nickel Forms

Humans can be exposed to many different forms of nickel in the environment. Nickel compounds can be grouped into the four general categories of soluble, sulfidic, oxidic, and metallic nickel, with the latter three categories consisting of compounds that are insoluble or slightly soluble (Goodman *et al.*, 2009). In the evidence review document for nickel, it was acknowledged that the various nickel compounds differ in their toxicity; however, CalOEHHA (2018) incorrectly stated that the least toxic forms to humans are the soluble nickel salts and the most toxic forms are the sulfidic and oxidic forms. While this is true for respiratory carcinogenicity after inhalation exposure, for general toxicity it has been shown in both acute and chronic experimental animal studies that the opposite is true; the soluble nickel salts are the *most* toxic, and the insoluble nickel oxides are the *least* toxic (ATSDR, 2005; Goodman *et al.*, 2011).

The majority of the epidemiology studies reviewed by CalOEHHA (2018) do not specify the nickel compound(s) being evaluated for associations with reproductive or developmental outcomes. This is because measurements of individual exposures to nickel compounds using biological samples (such as blood, urine, or hair) do not differentiate among nickel forms. With regard to all the studies that evaluated exposures to nickel in ambient air, nickel is predominantly found in suspended particulate matter (and thus also in soil, dust, and food) in the form of both oxides and sulfates (US EPA, 1986; ATSDR, 2005; CalOEHHA, 2012). For non-occupationally exposed study participants, the majority of nickel measured in blood or urine is derived from the diet (De Brouwere *et al.*, 2012). Only a few of the epidemiology studies evaluated occupational exposures, including in nickel refineries, which can be to multiple forms of nickel (Goodman *et al.*, 2009), and in welders exposed to nickel and other metals. Nickel in welding fumes is mostly present as nanometer-sized, complex metal oxides (*i.e.*, spinels).

## 3.2 Risk-of-Bias Analysis

To evaluate the risk of bias for each study, we used the NTP Office of Health Assessment and Translation (OHAT) Risk of Bias Rating Tool (NTP, 2015b), which aids in the assessment of a study's internal validity (*i.e.*, whether the design and conduct of the study compromised the credibility of any reported link between exposure and outcome). The OHAT Risk of Bias Rating Tool was developed using recent guidance from multiple organizations such as the Agency for Healthcare Research and Quality (AHRQ), Cochrane, the CLARITY Group at McMaster University, and the Navigation Guide, and comments from the public, technical advisors, and staff at other federal agencies (NTP, 2015b).

Using this tool, we assessed potential sources of bias using a set of questions, with detailed criteria provided under each question that are specific for each study design (*e.g.*, cohort, case-control, cross-sectional). These criteria define the aspects of study design, conduct, and reporting that are used to assign a risk-of-bias rating for each question. For epidemiology studies, the questions were divided into three key domains (exposure assessment, outcome assessment, and confounding), as well as three other risk-of-bias domains (selection bias, attrition bias, and statistical methods), and three domains specific to the study types and outcomes being reviewed (exposure levels, form of nickel, and temporality). The questions and criteria are specific enough that if different investigators applied them to the studies reviewed here, it is highly likely that they would assign the same risk of bias ratings as we did to each study. The specific questions and criteria for each of the nine domains are presented in Table 3.

We assigned risk-of-bias ratings to the 40 studies for each of the nine domains (Table 4). We then used the guidance from the NTP *Handbook for Conducting a Literature-based Health Assessment Using OHAT Approach for Systematic Review and Evidence Integration* (herein, the "OHAT Handbook;" NTP, 2015a) for dividing studies into three tiers of study quality based on their risk-of-bias ratings across domains. In this approach, studies are divided into tiers of increasing risk of bias as follows:

- Tier 1 – A study must be rated as "definitely low" or "probably low" risk of bias for all key domains AND have most other risk of bias domains as "definitely low" or "probably low."
- Tier 2 – Study does not meet the criteria for Tier 1 or Tier 3.
- Tier 3 – A study must be rated as "definitely high" or "probably high" risk of bias for all key domains AND have most other risk of bias domains as "definitely high" or "probably high."

As indicated in Table 4, using the OHAT Handbook approach resulted in all 40 studies being categorized as Tier 2. Tier 2 studies have an overall moderate risk of bias and are generally low quality, which decreases the reliability of their results. In general, most of the studies did not employ an appropriate statistical approach to assess potential confounding, utilized area-level exposure measurements, and were not able to assess the temporal relationship between nickel exposure and the outcome of interest, indicating a high risk of bias in these domains. We note, however, that even though all studies were categorized as Tier 2, there was variability in the level of risk of bias among studies, with some studies having a higher or lower risk of bias across more domains than others. The results of studies with a lower risk of bias across the key domains of exposure assessment, outcome assessment, and confounding are likely more reliable than studies with a higher risk of bias across these domains.

Below, we evaluate the results of the studies in the context of the factors that contributed to their moderate risk of bias and generally low quality. We did not fully incorporate study quality considerations into the discussion of all studies reporting null or negative results, however, because such results are not supportive of a causal association. Instead, these factors are shown in Tables 1 and 2.

### 3.3 Studies of Female Reproductive Outcomes

CalOEHHA (2018) reviewed three studies that assessed potential associations between nickel exposure and female reproductive outcomes. Each study examined different outcomes, so the consistency of findings across studies cannot be evaluated. Two of the studies reported null associations. Bloom *et al.* (2011) reported no association between blood nickel levels and time to pregnancy, and Maduray *et al.* (2017) reported no associations between hair or serum nickel concentrations and preeclampsia. Zheng *et al.* (2015) evaluated associations between serum nickel concentrations and polycystic ovary syndrome (PCOS), as well as multiple clinical chemistry parameters, including sex hormone levels. The authors reported statistically significantly higher serum nickel concentrations in PCOS cases compared to controls, and a statistically significant decrease in sex hormone binding globulin (SHBG) levels with increasing serum nickel concentrations. There were no associations between serum nickel concentrations and other clinical chemistry parameters that would be expected to change in relation to SHBG, however, including estradiol, testosterone, insulin, glucose, and cholesterol. Given the factors that contributed to the moderate risk of bias for this study (particularly a lack of accounting for important confounders, as well as likely selection bias and an inability to assess the temporal relationship between nickel exposure and the outcomes evaluated), the reported associations between nickel exposure and PCOS or alterations in SHBG levels need to be confirmed in other studies before they can be considered to support a hazard listing for nickel as a female reproductive toxicant. Overall, the three studies reviewed by CalOEHHA (2018) do not provide evidence for a causal association between exposure to nickel compounds and adverse female reproductive outcomes. As each of these studies measured nickel concentrations in non-occupational participants, none included exposures to nickel metal.

### 3.4 Studies of Male Reproductive Outcomes

CalOEHHA (2018) reviewed nine studies evaluating potential associations between nickel exposure and male reproductive outcomes. None of these studies accounted for important potential confounding variables, employed appropriate statistical approaches, or were able to assess temporal relationships given their cross-sectional design. As noted above, one of these studies (Slivkova *et al.* 2009) did not actually evaluate associations between nickel exposure and any reproductive outcome, and should not be included in an evaluation of the potential reproductive toxicity of nickel. The remaining eight studies evaluated associations between nickel in serum, semen, or urine and the outcomes of circulating hormone levels, sperm DNA damage, or sperm function parameters. While hormone levels and sperm DNA damage may or may not be indicative of adverse effects on male reproduction, the sperm function parameters are more direct indicators of adverse effects, such as infertility.

Zeng *et al.* (2013) reported no association between urinary nickel levels and plasma testosterone, whereas Sancini *et al.* (2014) reported a statistically significant decrease in plasma testosterone with increasing urinary nickel levels. Wang *et al.* (2016) reported a statistically significant decrease in the ratio of testosterone to luteinizing hormone (LH) with increasing urinary nickel levels, but no effect of nickel on levels of testosterone or other sex hormones. The authors also reported no association between urinary nickel levels and markers of sperm DNA damage (comet assay tail length, distributed moment, and tail percent). By contrast, Zhou *et al.* (2016) reported a statistically significant association between increasing urinary nickel levels and increased comet assay tail length in sperm, but no association with distributed moment or tail percent. It is notable that the populations studied by Zeng *et al.* (2013) and Wang *et al.* (2016) consisted of male partners in couples undergoing infertility assessment in China, and those studied by Zhou *et al.* (2016) were infertile Chinese men; thus, the results of these studies are not generalizable to the general US population.

Regarding associations between nickel exposure and sperm functional parameters, two studies reported statistically significant decreases in sperm motility (Danadevi *et al.*, 2003; Zafar *et al.*, 2015), whereas two others reported no effects on motility (Skalnaya *et al.*, 2015; Zeng *et al.*, 2015). Danadevi *et al.* (2003) also reported significantly decreased sperm vitality associated with nickel exposure, whereas Skalnaya *et al.* (2015) reported no effect of nickel on vitality. Results for sperm head abnormalities were also inconsistent between studies (Danadevi *et al.*, 2003; Zeng *et al.*, 2015). Skalnaya *et al.* (2015) reported a statistically significant association between semen nickel levels and decreased ejaculate volume using the Mann-Whitney U test, but a correlation analysis did not confirm these results. Zafar *et al.* (2015) reported significantly decreased sperm count in association with nickel exposure, whereas the studies by Danadevi *et al.* (2003), Skalnaya *et al.* (2015), and Zeng *et al.* (2015) found no association between nickel and sperm count. The populations studied by Zafar *et al.* (2015) and Zeng *et al.* (2015) consisted of male partners in couples undergoing infertility assessment in Pakistan and China, respectively. In addition, the studies by Zafar *et al.* (2015) and Skalnaya *et al.* (2015) used inappropriate statistical methods, reducing the reliability of their results.

Overall, the results for each of the male reproductive outcomes examined were inconsistent across studies, and do not support a causal association with nickel exposure. More importantly, because all the studies were found to have a moderate risk of bias, the validity of their results is questionable, and they do not support a hazard listing for nickel or nickel compounds as male reproductive toxicants.

### 3.5 Studies of Developmental Outcomes

CalOEHHA (2018) reviewed 28 studies evaluating potential associations between nickel exposure and various developmental outcomes, including birth defects, low birth weight, adverse pregnancy outcomes, autism spectrum disorder (ASD), early-life cancers, and DNA damage. Some of these studies had a lower risk of bias across more key domains than others, so their results may be more reliable than studies with a higher risk of bias across more key domains, as discussed below.

#### *Birth Defects*

Of the eight studies of nickel associations with birth defects reviewed by CalOEHHA (2018), one (Huang *et al.*, 2011) did not evaluate statistical associations between nickel exposure and any health outcome, and should not be included in an evaluation of the potential developmental toxicity of nickel. Of the remaining seven studies, two reported statistically significant associations with birth defects (Chashschin *et al.*, 1994; Zheng *et al.*, 2012), whereas four reported no associations between nickel exposure and birth defects (Friel *et al.*, 2005; Vaktskjold *et al.*, 2006, 2008b; Manduca *et al.*, 2014) and one reported a statistically significant negative (*i.e.*, protective) association with nickel exposure (Yan *et al.*, 2017). It is important to note that one of the positive studies (Chashschin *et al.*, 1994) includes a disclaimer from the journal editors stating the following: "Although the results are incompletely documented and thus must be considered inconclusive, they identify a concern that requires a more comprehensive and quantitative epidemiologic investigation." In addition, the cohort of female workers studied by Chashschin *et al.* (1994) was subsequently investigated more thoroughly by Vaktskjold *et al.* (2006, 2008b), who did not reproduce the earlier positive findings.

The studies by Vaktskjold *et al.* (2006, 2008b) measured concentrations of water-soluble nickel in aerosols at a Russian nickel refinery, in conjunction with urinary nickel concentrations, to estimate low and high nickel exposure categories. Similarly, Chashschin *et al.* (1994) measured water-soluble nickel sulfate aerosol concentrations in two specific areas of the refinery. Other nickel compounds with potential exposures in the refinery, such as insoluble forms of nickel, were not discussed and therefore not accounted for in these exposure assessments. Regardless, the studies by Vaktskjold *et al.* (2006, 2008b) reported no

associations between nickel exposures that were more than 1,000-fold higher than in ambient air and birth defects.

Although all the studies of nickel associations with birth defects have a moderate risk of bias because of inappropriate statistical methods and a lack of accounting for important confounders, three of the studies reporting null or negative associations assessed exposures and outcomes using well-established methods, had low probability for both selection and attrition bias, and were designed to directly assess temporality of exposure and outcome, increasing the reliability of their results (Vaktskjold *et al.*, 2006, 2008b; Yan *et al.*, 2017). Because the majority of the studies reported null or negative results (including those with more reliable results), they do not support a causal association between exposure to nickel and/or nickel compounds and birth defects.

### *Low Birth Weight*

Ten studies evaluated nickel associations with measures of low birth weight. Four of these studies reported statistically significant, positive associations between nickel exposure and lower birth weight (Bell *et al.*, 2010; Ebisu and Bell, 2012; Basu *et al.*, 2014; Laurent *et al.*, 2014), and one study reported a borderline statistically significant association with lower birth weight and a significant association with decreased newborn head circumference (Pederson *et al.*, 2016). Four studies reported no associations between nickel exposure and birth weight (Odland *et al.*, 1999, 2004; McDermott *et al.*, 2014; Hu *et al.*, 2015), and one study reported a negative association between nickel exposure and low birth weight (Vaktskjold *et al.*, 2007).

Given that the studies by Bell *et al.* (2010), Ebisu and Bell (2012), and Vaktskjold *et al.* (2007) have a lower risk of bias across more domains than the other studies evaluating birth weight, their results are likely more reliable. However, an independent analysis indicates that the study by Vaktskjold *et al.* (2007) had adequate statistical power to detect the effects on low birth weight reported by Ebisu and Bell (2012) (if they are indeed causal) at nickel exposure concentrations 40-fold lower than those estimated for the workers in the study (see S. Seilkop comments, submitted separately), indicating the importance of testing hypotheses generated by univariate analyses in multi-pollutant studies such as those by Ebisu and Bell (2012) and Bell *et al.* (2000). Given this analysis, as well as the inconsistency of the results for low birth weight across studies (even those of similar reliability), the studies evaluating nickel associations with low birth weight do not provide evidence to support a causal association.

### *Autism Spectrum Disorder*

Three studies evaluated associations between nickel exposure and ASD prevalence, with one reporting no association (Kalkbrenner *et al.*, 2010) and two studies reporting statistically significant associations (Windham *et al.*, 2006; Roberts *et al.*, 2013). The latter two studies are limited by a lack of confidence in the exposure assessment, a lack of accounting for important confounders, and inappropriate statistics, so it is unclear whether nickel exposures were adequately measured and the positive results are likely attributable to bias or confounding. Together, these three studies do not provide evidence for a causal association between nickel exposure and ASD.

### *DNA Oxidative Damage and Early-Life Cancers*

One study reported a statistically significant association between nickel exposure and DNA oxidative damage in umbilical cord plasma (Ni *et al.*, 2014). Three other studies evaluated risks of early-life cancers, reporting no associations between nickel exposure and development of neuroblastoma (Heck *et al.*, 2013) or testicular germ cell tumors (Togawa *et al.*, 2016), and a statistically significant association between nickel exposure and increased risk of retinoblastoma (Heck *et al.*, 2015). As the outcomes of DNA

oxidative damage and retinoblastoma risk were only evaluated in one study each, and these studies are limited by several factors including a lack of accounting for confounders, further studies of potential associations between nickel exposure and these outcomes are needed before they can be considered as supportive evidence for a causal association.

### *Adverse Pregnancy Outcomes*

Four studies evaluated adverse pregnancy outcomes (including spontaneous abortion and premature birth) and three reported no associations with nickel exposure (Vaktkjold *et al.*, 2008a; Zheng *et al.*, 2014; Manduca *et al.*, 2014), whereas one reported an increased risk of spontaneous abortion in nickel-exposed female workers (Chashschin *et al.*, 1994). As noted above, the study by Chashschin *et al.* (1994) was not well documented, and a more recent study of the same cohort did not reproduce the positive findings for spontaneous abortion (Vaktkjold *et al.*, 2008a). One study reported no association between nickel exposure and pneumonia in early life (Fuentes *et al.*, 2014). As each of these studies evaluated different outcomes (with the exception of the inconsistent results for spontaneous abortion in two studies), they do not provide strong evidence for or against causal associations with nickel exposure.

## **3.6 Summary**

Overall, the results of a risk-of-bias analysis and study evaluation indicate that the epidemiology studies reviewed by CalOEHHA (2018) do not provide evidence that nickel and/or nickel compounds present a reproductive or developmental hazard. All reviewed studies had a moderate risk of bias, indicating generally low quality, due to the lack of appropriate statistical approaches to assess potential confounding, the use of area-level exposure measurements, and an inability to assess the temporal relationship between nickel exposure and the outcome of interest. The majority of studies evaluated exposures to soluble and oxidic forms of nickel (*i.e.*, in ambient air or welding fumes), and the results across the various reproductive and developmental outcomes examined were largely inconsistent or null. Workers in the refinery studies had additional exposures to sulfidic and metallic nickel, and the results of these studies were largely null or not reproducible in more reliable studies. Overall, the epidemiology studies do not provide clear evidence for associations between any form of nickel and any particular reproductive or developmental outcome.

## 4 Conclusions

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In its review of the evidence for hazard identification for nickel compounds, CalOEHHA (2018) did not follow a systematic approach and gave more weight to positive studies than those reporting null or negative associations, regardless of study quality or risk of bias. This led to an evaluation that does not represent the state of the science regarding the potential reproductive and developmental toxicity of nickel compounds. This will also limit the ability of DARTIC to form scientifically defensible opinions regarding the reproductive hazard potential of nickel compounds, making it difficult for DARTIC to determine whether nickel and nickel compounds meet the CalOEHHA criteria for listing as a known reproductive toxicant.

In a risk-of-bias analysis of the epidemiology studies reviewed by CalOEHHA (2018) using the NTP OHAT Risk of Bias Rating Tool, we found that all studies have an overall moderate risk of bias, indicating generally low quality, due to the lack of appropriate statistical approaches to assess potential confounding, the use of area-level exposure measurements in many studies, and an inability to assess the temporal relationship between nickel exposure and the outcome of interest. Results across the various reproductive and developmental outcomes examined were largely inconsistent or null, with no clear evidence for associations between any form of nickel and any particular outcome. Overall, the epidemiology studies do not provide evidence that nickel or nickel compounds present a reproductive or developmental hazard.

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# Tables

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**Table 1 Characteristics of Epidemiology Studies Evaluating Nickel Exposure and Reproductive and Developmental Effects that Impact Study Quality**

Study	Outcome Category	Study Design	Study Population		Temporality	Exposure Assessment			Outcome Ascertainment	Potential Confounders Considered	Statistical Analysis		
			Selection Bias	Sample Size		Personal Measurement	Metric Used	Form of Nickel			Statistical Approach	Dose-Response Assessed	Dose-Response Relationship with Ni
Bloom et al., 2011	Female reproductive	Cohort	Population-based	80	Yes	Yes	Whole blood	NR. Blood Ni concentration analyzed using ICP-MS.	Home pregnancy test	Yes	Cox proportional hazards models	Yes	Yes
Zheng et al., 2015	Female reproductive	Case-control	High risk, Hospital-based	201	No	Yes	Serum	NR. Serum Ni concentration analyzed using ICP-MS.	Blood sample	No	Mann-Whitney U (PCOS)	Yes	Yes
										Yes	Linear regression (Hormone levels)	Yes	Yes
Maduray et al., 2017	Female reproductive	Case-control	High risk, Hospital-based	66	No	Yes	Pubic hair; serum	NR. Hair and serum Ni concentration analyzed using ICP-OES.	Medical records	No	Mann-Whitney U, t-test	No	NA
Danadevi et al., 2003	Male reproductive	Cross-sectional	High risk, Occupation	114	No	Yes	Whole blood	NR. Blood Ni concentration analyzed using ICP-MS.	Ejaculate	No	Linear regression	Yes	Yes, for progressive motility, tail defects, and vitality
Slivkova et al., 2009	Male reproductive	Cross-sectional	High risk, Hospital-based	47	No	Yes	Semen	NR. Ni quantification method was not clearly reported.	Ejaculate	No	r	No	NA
Zeng et al., 2013	Male reproductive	Cross-sectional	High risk, Hospital-based	118	No	Yes	Urine, creatinine-adjusted	NR. Urinary Ni concentration analyzed using ICP-MS.	Peripheral blood sample	Yes	Linear regression	Yes	No
Sancini et al., 2014	Male reproductive	Cross-sectional	High risk, Occupation	274	No	Yes	Urine, creatinine-adjusted	NR. Urinary Ni determined by complexation with APDC and atomic absorption analysis in graphite furnace.	Blood sample	Yes	Linear regression	Yes	Yes
Skalnaya et al., 2015	Male reproductive	Cross-sectional	High risk, insufficient information	148	No	Yes	Semen	NR. Semen Ni concentration analyzed using ICP-MS.	Ejaculate	No	Mann-Whitney U, r	No	NA

Study	Outcome Category	Study Design	Study Population		Temporality	Exposure Assessment			Outcome Ascertainment	Potential Confounders Considered	Statistical Analysis		
			Selection Bias	Sample Size		Personal Measurement	Metric Used	Form of Nickel			Statistical Approach	Dose-Response Assessed	Dose-Response Relationship with Ni
Zafar et al., 2015	Male reproductive	Cross-sectional	High risk, hospital-based	75	No	Yes	Semen	NR. Semen Ni concentration analyzed using ICP-MS.	Ejaculate	No	One-way ANOVA, r	No	NA
Zeng et al., 2015	Male reproductive	Cross-sectional	High risk, hospital-based	394	No	Yes	Urine, creatinine-adjusted	NR. Urinary Ni concentration analyzed using ICP-MS.	Ejaculate	Yes	Logistic regression, Linear regression	Yes	Yes, for percent and sperm abnormal head
Wang et al., 2016	Male reproductive	Cross-sectional	High risk, hospital-based	551 (serum hormone), 460 (spermatozoa apoptosis), 516 (sperm DNA damage)	No	Yes	Urine, creatinine-adjusted	NR. Urinary Ni concentration analyzed using ICP-MS.	Semen sample, blood sample	Yes	Linear regression	Yes	Yes, for some endpoints
Zhou et al., 2016	Male reproductive	Cross-sectional	High risk, hospital-based	207	No	Yes	Urine, creatinine-adjusted	NR. Urinary Ni concentration analyzed using ICP-MS.	Ejaculate	Yes	Linear regression	Yes	Yes, for Comet tail length
Chashschin et al., 1994	Developmental	Cross-sectional	High risk, Occupation	698	No	Yes	Urine, 24-hour	Nickel sulfate aerosols.	Medical records	Yes	POR	No	NA
Odland et al., 1999	Developmental	Cross-sectional	High risk, Occupation	265	No	Yes	Urine	NR. Urinary Ni concentration analyzed using electrothermal atomic absorption spectrometry.	Medical records	Yes	Linear regression	Yes	No
Odland et al., 2004	Developmental	Cross-sectional	High risk, Occupation	262	No	Yes	Blood Urine Placenta	NR.	Medical records	No	Linear regression	Yes	No
Friel et al., 2005	Developmental	Cross-sectional	High risk, hospital-based	55	No	Yes	Liver, kidney, diaphragmatic muscle, sciatic nerve, pancreas	NR. Ni concentration analyzed using ICP-MS.	Medical records	No	t-test	No	NA
Vaktskjold et al., 2006	Developmental	Cohort	High risk, Occupation	23,141	Yes	Yes	Employment, urine, air	Water-soluble nickel compounds and solvents.	Birth Registry	Yes	Logistic regression	Yes	No

Study	Outcome Category	Study Design	Study Population		Temporality	Exposure Assessment			Outcome Ascertainment	Potential Confounders Considered	Statistical Analysis		
			Selection Bias	Sample Size		Personal Measurement	Metric Used	Form of Nickel			Statistical Approach	Dose-Response Assessed	Dose-Response Relationship with Ni
Windham et al., 2006	Developmental	Case-control	Population-based	941	No	No	1996 US EPA HAPs data	NR. HAPs concentrations estimated from Gaussian air dispersion model that combines emissions inventories from mobile, point and area sources with data on local meteorology, chemical decay rates, secondary formation, and deposition.	Medical records	Yes	Logistic regression	Yes	Yes
Vaktskjold et al., 2007	Developmental	Cohort	High risk, Occupation	22,836	Yes	Yes	Employment, urine, air	Water-soluble nickel subfraction of respirable aerosol fraction.	Birth Registry	Yes	Logistic regression	Yes	Yes
Vaktskjold et al., 2008a	Developmental	Case-control	High risk, Occupation	1,875	Yes	Yes	Employment, urine, air	Water-soluble nickel subfraction of respirable aerosol fraction.	Birth Registry, Questionnaire	Yes	Logistic regression	Yes	No
Vaktskjold et al., 2008b	Developmental	Cohort	High risk, Occupation	22,965	Yes	Yes	Employment, urine, air	Water-soluble nickel subfraction of respirable aerosol fraction.	Birth Registry	Yes	Logistic regression	Yes	No
Bell et al., 2010	Developmental	Cohort	Population-based	76,788	Yes	No	County-wide exposure estimates via ambient air monitors	Ni as an oil-combustion-associated element of PM <sub>2.5</sub> determined by X-ray fluorescence.	Birth certificate	Yes	Logistic regression, Linear regression	Yes	Yes

Study	Outcome Category	Study Design	Study Population		Temporality	Exposure Assessment			Outcome Ascertainment	Potential Confounders Considered	Statistical Analysis		
			Selection Bias	Sample Size		Personal Measurement	Metric Used	Form of Nickel			Statistical Approach	Dose-Response Assessed	Dose-Response Relationship with Ni
Kalkbrenner et al., 2010	Developmental	Case-control	Population-based	3,212	Yes	No	US EPA HAPs data (NATA-1996)	Ni compounds as HAPs. HAPs concentrations estimated from Gaussian air dispersion, based on emissions inventory information for point and area sources as well as data on local meteorology and secondary pollutant formation.	Developmental records	Yes	Logistic regression	Yes	No
Huang et al., 2011	Developmental	Ecologic	Population-based	NR	No	No	Mixed village soil sample	NR. Soil Ni concentration analyzed using ICP-MS.	Physician verification	NR	Poisson regression	Yes	Yes
Zheng et al., 2012	Developmental	Ecologic	Population-based	379	No	No	Village soil sample	NR. Soil Ni concentration analyzed using ICP-MS.	Birth records	Yes	Poisson regression	Yes	Yes
Ebisu and Bell, 2012	Developmental	Cohort	Population-based	1,207,800	Yes	No	County-wide exposure estimates <i>via</i> ambient air monitors	Ni as an element of PM <sub>2.5</sub> . Average level of exposure calculated during gestation and each trimester.	Birth certificate	Yes	Logistic regression	Yes	Yes
Heck et al., 2013	Developmental	Case-control	Population-based	14,677	Yes	No	Measurements from nearest ambient air monitors	Ni as an air toxic.	California Cancer Registry	Yes	Logistic regression	Yes	No
Roberts et al., 2013	Developmental	Nested case-control	High risk, Occupation	22,426	Yes	No	US EPA HAPs data (NATA-1990, 1996, 1999, 2002)	Ni as a HAP.	Questionnaire, Telephone administration of the ADI-R	Yes	Logistic regression	Yes	Yes
Basu et al., 2014	Developmental	Cohort	Population-based	646,296	Yes	No	Measurements <i>via</i> ambient air monitors	Ni as an element of PM <sub>2.5</sub> .	Birth records	Yes	Logistic regression, Linear regression	Yes	Yes

Study	Outcome Category	Study Design	Study Population		Temporality	Exposure Assessment			Outcome Ascertainment	Potential Confounders Considered	Statistical Analysis		
			Selection Bias	Sample Size		Personal Measurement	Metric Used	Form of Nickel			Statistical Approach	Dose-Response Assessed	Dose-Response Relationship with Ni
Fuertes et al., 2014	Developmental	Meta-analysis of cohorts	Population-based	15,980	Yes	Yes	LUR estimates at residence	Ni as an element of PM <sub>2.5</sub> and PM <sub>10</sub> . Annual average exposure estimated.	Parental reports	Yes	Logistic regression	Yes	Yes
Laurent et al., 2014	Developmental	Cohort	Population-based	960,945	Yes	No	4 × 4 km exposure estimates via CTM	Ni as an element of primary PM. Simulated PM concentrations calculated for PM <sub>2.5</sub> and PM <sub>0.1</sub> .	Birth certificate	Yes	Generalized additive models	Yes	Yes
Manduca et al., 2014	Developmental	Case-control	High risk, hospital-based	69	Yes	Yes	Hair	NR. Hair Ni concentration analyzed using DRC-ICP-MS.	Medical records	No	Wilcoxon-Mann-Whitney test	No	NA
McDermott et al., 2014	Developmental	Cohort	High risk, Minority	9,920	Yes	Yes	Kriging soil estimates at residence	NR. Soil Ni concentration analyzed by an independent analytical laboratory.	Birth certificate	Yes	Generalized additive models	Yes	No
Ni et al., 2014	Developmental	Cross-sectional	Population-based	201	No	Yes	Umbilical cord blood	NR. Blood Ni concentration analyzed using GFAAS.	Plasma sample measurements	Yes	Linear regression	Yes	Yes
Zheng et al., 2014	Developmental	Case-control	Population-based	179	No	Yes	Umbilical cord blood	NR. Blood Ni concentrations analyzed using ICP-MS.	Medical records	No	Mann-Whitney U	No	NA
Heck et al., 2015	Developmental	Case-control	Population-based	30,704	Yes	No	Measurements via nearest ambient air monitor	Ni as an air toxic.	California Cancer Registry	Yes	Logistic regression	Yes	Yes
Hu et al., 2015	Developmental	Cross-sectional	High risk, hospital-based	81	No	Yes	Maternal and cord blood	NR. Blood Ni concentrations analyzed using ICP-MS.	Medical records	Yes	Linear regression	Yes	No
Pedersen et al., 2016	Developmental	Meta-analysis	Population-based	34,923	Yes	Yes (except for Lithuanian and Swedish cohorts)	LUR estimates at residence (except for Lithuanian and Swedish cohorts)	Ni as an element of PM <sub>2.5</sub> and PM <sub>10</sub> . Annual average exposure estimated.	Birth records/parental reports	Yes	Logistic regression; Linear regression	Yes	No
Togawa et al., 2016	Developmental	Case-control	Population-based	34,376	Yes	Yes	JEM	NR. Ni exposure determined using Nordic JEMs.	Nationwide cancer registries	Yes	Logistic regression	Yes	No

Study	Outcome Category	Study Design	Study Population		Temporality	Exposure Assessment			Outcome Ascertainment	Potential Confounders Considered	Statistical Analysis		
			Selection Bias	Sample Size		Personal Measurement	Metric Used	Form of Nickel			Statistical Approach	Dose-Response Assessed	Dose-Response Relationship with Ni
Yan et al., 2016	Developmental	Case-control	High risk, hospital-based	452	Yes	Yes	Hair	NR. Hair Ni concentration analyzed using ICP-MS.	Medical records	Yes	Logistic regression	Yes	Yes

Notes:

ADI-R = Autism Diagnostic Interview - Revised; ANOVA = Analysis of Variance; CTM = Chemical Transport Models; DNA = Deoxyribonucleic Acid; DRC-ICP-MS = Dynamic Reaction Cell Inductively Coupled Plasma Mass Spectrometry; GFAAS = Graphic Furnace Atomic Absorption Spectrometry; HAP = Hazardous Air Pollutant; ICP-MS = Inductively Coupled Plasma Mass Spectrometry; ICP-OES = Inductively Coupled Plasma-Optical Emission Spectrometry; JEM = Job-Exposure Matrix; LUR = Land Use regression; NA = Not Applicable; NATA = National Air Toxics Assessment; Ni = Nickel; NR = Not Reported; PCOS= Polycystic Ovary Syndrome; PM = Particulate Matter; POR = Prevalence Odds Ratio; R = Correlation Coefficient; US EPA = United States Environmental Protection Agency.

**Table 2 Results of Epidemiology Studies Evaluating Nickel Exposure and Reproductive and Developmental Effects**

Study	Outcome Category	Study Design	Sample Size	Exposure Metric	Outcome Assessed	Effect Measure	Unit of Measure	Effect Estimate	95% CI	P for Risk Estimates
Bloom et al., 2011	Female reproductive	Cohort	80	Whole blood	Time to pregnancy	% change	Per IQR increment	-8.6	NR	0.79
Zheng et al., 2015	Female reproductive	Case-control	201	Blood serum	PCOS	Difference in medians (µg/L)	NA	0.41*	NR	0.000
					FSH	% change	Per ng/mL increment	0.736	-2.784, 4.256	0.681
					LH		5.333	-2.201, 12.866	0.164	
					Estradiol		-4.204	-9.654, 1.247	0.13	
					Prolactin		3.215	-2.841, 9.270	0.296	
					T		3.168	-2.569, 8.904	0.278	
					Progesterone		-2.025	-9.557, 5.508	0.597	
					TSH		-6.821	-15.960, 2.319	0.143	
					DHEA-S		3.234	-0.452, 6.919	0.085	
					SHBG		-12.602	-24.083, -1.122	0.032	
					Fasting insulin		2.655	-2.866, 8.177	0.344	
					Fasting glucose		0.978	-0.437, 2.393	0.175	
					Cholesterol		0.783	-1.149, 2.716	0.425	
					Triglycerides		0.368	-5.853, 6.589	0.907	
Low-density lipoprotein cholesterol		1.38	-1.461, 4.221	0.339						
High-density lipoprotein cholesterol		0.41	-2.150, 2.971	0.752						
Maduray et al., 2017	Female reproductive	Case-control	66	Pubic hair	Pre-eclampsia	Difference in medians (µg/g)	NA	-1.54*	NR	0.85
				Serum		Difference in medians (mg/L)	NA	-0.12*	NR	0.16
			114	Blood serum	Sperm count			-0.352	NR	0.067

Study	Outcome Category	Study Design	Sample Size	Exposure Metric	Outcome Assessed	Effect Measure	Unit of Measure	Effect Estimate	95% CI	P for Risk Estimates	
Danadevi et al., 2003	Male reproductive	Cross-sectional			Rapid linear progressive motility	Mean change	Per µg/L increment	-0.381		0.045	
					Slow/non-linear progressive motility			0.386		0.042	
					Nonprogressive motility			0.141		0.474	
					Immotility			0.007		0.971	
					Normal morphology			-0.032		0.872	
					Head defects			-0.145		0.462	
					Mid-piece defects			0.067		0.734	
					Tail defects			0.485		0.036	
Vitality	-0.420	0.026									
Slivkova et al., 2009	Male reproductive	Cross-sectional	47	Semen	Knob-twisted flagellum, separated flagellum, flagellum torso, broken flagellum, retention of cytoplasmic drop, acrosomal changes, large heads, small heads, flagellum ball, and other pathological forms.	r	NA	NR	NA	NR	
Zeng et al., 2013	Male reproductive	Cross-sectional	118	Urine, creatinine-adjusted	Plasma testosterone	Mean change (ng/dL)	1st quartile	REF		0.14 <sup>#</sup>	
							2nd quartile	-0.86			-81.25, 79.53
							3rd quartile	-83.79			-163.85, -3.74
							4th quartile	-36.35			-116.31, 43.61

Study	Outcome Category	Study Design	Sample Size	Exposure Metric	Outcome Assessed	Effect Measure	Unit of Measure	Effect Estimate	95% CI	P for Risk Estimates					
Sancini et al., 2014	Male reproductive	Cross-sectional	274	Urine, creatinine-adjusted	Plasma testosterone	Mean log change (ng/mL)	Per unit increment (log)	-0.466	NR	0.000					
Skalnaya et al., 2015	Male reproductive	Cross-sectional	148	Semen	Ejaculate volume <1.5 mL	Mann-Whitney U	NA	NR	NA	0.015					
						r		-0.123			>0.05				
					Total sperm count < 39 ×10 <sup>6</sup>	Mann-Whitney U	NA	NR	NA	0.452					
						r		-0.069			>0.05				
					Sperm count < 15 × 10 <sup>6</sup> per 1 mL	Mann-Whitney U	NA	NR	NA	0.211					
						r		0.005			>0.05				
					Progressive sperm motility < 32%	Mann-Whitney U	NA	NR	NA	0.708					
						r		-0.041			>0.05				
					Sperm vitality < 58	Mann-Whitney U	NA	NR	NA	0.872					
						r		-0.049			>0.05				
					Zafar et al., 2015	Male reproductive	Cross-sectional	75	Semen	Sperm count	r	NA	-0.26	NA	<0.05
										Sperm motility	r	NA	-0.33	NA	<0.05
Semen volume	r	NA	-0.44	NA						<0.05					
Sperm concentration	Difference in means (ppb)	NA	NR	NR						0.01					
Zeng et al., 2015	Male reproductive	Cross-sectional	394	Urine, creatinine-adjusted	Sperm concentration	OR	1st quartile	REF	0.38, 3.01	0.84 <sup>#</sup>					
							2nd quartile	1.06							
							3rd quartile	0.96			0.34, 2.73				
							4th quartile	1.14			0.41, 3.17				
					Sperm motility	OR	1st quartile	REF	0.45, 1.44	0.19 <sup>#</sup>					
							2nd quartile	0.8							

Study	Outcome Category	Study Design	Sample Size	Exposure Metric	Outcome Assessed	Effect Measure	Unit of Measure	Effect Estimate	95% CI	P for Risk Estimates					
							3rd quartile	0.77	0.43, 1.39						
							4th quartile	0.67	0.37, 1.02						
					Sperm count	OR	1st quartile	REF	0.55 <sup>#</sup>						
							2nd quartile	1.1		0.39, 3.12					
							3rd quartile	0.84		0.28, 2.48					
							4th quartile	0.79		0.27, 2.30					
					Sperm normal morphology	% change	1st quartile	REF	0.86 <sup>#</sup>						
							2nd quartile	2.02		0.14, 3.90					
							3rd quartile	0.89		-0.99, 2.76					
							4th quartile	0.22		-1.66, 2.10					
					Percent abnormal head	% change	1st quartile	REF	0.03 <sup>#</sup>						
							2nd quartile	-1.65		-3.90, 0.60					
							3rd quartile	-1.65		-1.32, 3.16					
							4th quartile	-1.65		-0.57, 3.92					
					Sperm abnormal Head	% change	1st quartile	REF	0.01 <sup>#</sup>						
							2nd quartile	-1.62		-3.91, 0.67					
							3rd quartile	1.13		-1.27, 3.53					
							4th quartile	2.41		-0.09, 4.91					
					Wang et al., 2016	Male reproductive	Cross-sectional	551	Urine, creatinine-adjusted	Estradiol	% change	Quartiles	NR	NR	0.98 <sup>#</sup>
										FSH	% change	Quartiles			0.10 <sup>#</sup>
LH	% change	Quartiles	0.50 <sup>#</sup>												
SHBG	% change	Quartiles	0.86 <sup>#</sup>												
Total T	% change	Quartiles	0.30 <sup>#</sup>												
Total T/LH ratio	% change	Quartiles	0.02 <sup>#</sup>												
Total T/LH ratio	Mean change	Per µg/L increment (log)	0.003												
Total T/LH ratio (co-adjusted for multiple metals)	% change	1st quartile	REF	0.03 <sup>#</sup>											
		2nd quartile	-1.7							-16, 13					
		3rd quartile	-8.3							-25, 6.2					
		4th quartile	-14		-32, 2										

Study	Outcome Category	Study Design	Sample Size	Exposure Metric	Outcome Assessed	Effect Measure	Unit of Measure	Effect Estimate	95% CI	P for Risk Estimates
			460	Urine, creatinine-adjusted	Annexin V+/PI-spermatozoa	% change	Quartiles	NR	NR	0.10 <sup>#</sup>
					PI+ spermatozoa	% change	Quartiles			0.98 <sup>#</sup>
					Annexin V-/PI-spermatozoa	% change	Quartiles			0.18 <sup>#</sup>
					Annexin V+/PI-spermatozoa (co-adjusted for multiple metals)	% change	1st quartile	REF	0.002	
						% change	2nd quartile	-6.2		-30, 15
						% change	3rd quartile	14		-7.3, 39
						% change	4th quartile	28		5.1, 55
			516	Urine, creatinine-adjusted	Comet tail percent	% change	Quartiles	NR	NR	0.81 <sup>#</sup>
					Comet tail length	% change	Quartiles			0.67 <sup>#</sup>
					Comet tail distributed moment	% change	Quartiles			0.94 <sup>#</sup>
Zhou et al., 2016	Male reproductive	Cross-sectional	207	Urine, creatinine-adjusted	Comet tail percent DNA	Mean change	Quartiles	NR	NR	0.13 <sup>#</sup>
					Comet tail length	Mean change (µm)	Quartiles			0.02 <sup>#</sup>
					Comet tail distributed moment	Mean change (µm)	Quartiles			0.78 <sup>#</sup>
					Comet tail length	Mean change (µm)	1st quartile	REF	0.049 <sup>#</sup>	
							2nd quartile	-0.58		-2.88, 1.71
							3rd quartile	-0.36		-2.71, 1.99
							4th quartile	2.95		0.34, 5.56
Chashschin et al., 1994	Developmental	Cross-sectional	698	Urine (24-hour)	Total defects	POR	NR	2.9	NR	NR
					Cardiovascular defects			6.1	NR	NR
					Musculoskeletal defects			1.9	NR	NR
					SA			1.8	NR	NR

Study	Outcome Category	Study Design	Sample Size	Exposure Metric	Outcome Assessed	Effect Measure	Unit of Measure	Effect Estimate	95% CI	P for Risk Estimates
Odland et al., 1999	Developmental	Cross-sectional	265	Maternal urine	BW	Mean change (g)	Per nmol/L increment	-1	-6, 5	> 0.05
					BMIC	Mean change (kg/m <sup>2</sup> )		0	-0.03, 0.004	> 0.05
Odland et al., 2004	Developmental	Cross-sectional	262	Blood, urine, placenta	BW	Mean change (g)	Per nmol/L increment	-1510	-3191, 170	> 0.05
					BMIC	Mean change (kg/m <sup>2</sup> )		-2.73	-7.49, 2.02	> 0.05
Friel et al., 2005	Developmental	Cross-sectional	55	Liver, kidney, diaphragmatic muscle, sciatic nerve, pancreas	Anencephaly	Difference in means (ppm)	NA	NR	NR	> 0.05
Vaktskjold et al., 2006	Developmental	Cohort	23,141	Employment, urine, air	Genital malformations	OR	Per unit increment in exposure category (Background, low, high)	0.81	0.52, 1.26	NR
						OR		Background	REF	NR
								Low	0.71	
						High	0.72	0.26, 1.95		
Windham et al., 2006	Developmental	Case-control	941	US EPA HAPS data (1996)	ASD	OR	Quartiles	1.46 <sup>a</sup>	1.04, 2.06	NR
Vaktskjold et al., 2007	Developmental	Cohort	22,836	Employment, urine, air	SGA	OR	Per unit increment in exposure category (Background, low, high)	0.84	0.75, 0.93	NR
Vaktskjold et al., 2008a	Developmental	Case-control	1,875	Employment, urine, air	SA (Questionnaire)	OR	Per unit increment in	1.14	0.95, 1.37	NR

Study	Outcome Category	Study Design	Sample Size	Exposure Metric	Outcome Assessed	Effect Measure	Unit of Measure	Effect Estimate	95% CI	P for Risk Estimates				
			5,045		SA (Birth Registry)	OR	exposure category (Background, low, high)	0.87	0.72, 1.06	NR				
			1,875		SA (Questionnaire)	OR	Background	REF		NR				
							Low	1.39	0.88, 2.19					
							High	1.27	0.87, 1.86					
			5,045		SA (Birth Registry)	OR	Background	REF	NR					
							Low	0.78		0.53, 1.64				
							High	0.8		0.53, 1.23				
			Vaktskjold et al., 2008b		Developmental	Case-control	22,965	Employment, urine, air	Musculoskeletal defects	OR	Per unit increment in exposure category (Background, low, high)	0.96	0.76, 1.21	NR
											Background	REF	NR	
Low	1.3	0.87, 1.93												
High	0.72	0.40, 1.29												
Bell et al., 2010	Developmental	Cohort	76,788	Air monitors	Small-at-term birth	% change	Per IQR increment	11	3, 19	NR				
					Birth weight	Mean change (g)		-7	-12, -3					
Kalkbrenner et al., 2010	Developmental	Case-control	3,212	US EPA HAPs data (1996)	ASD	OR	80th vs. 20th percentile (1.7 vs. 0.1 ng/m3)	1.1	0.6, 1.9	NR				
Huang et al., 2011	Developmental	Ecologic	NR	Soil	Neural tube defects	NR	NR	NR	NR	NR				
Zheng et al., 2012	Developmental	Ecologic	379	Soil	Birth defects	Change in the logs of expected counts	1st quartile	REF						
							2nd quartile	-0.39	-0.75, -0.05*	0.0265				
							3rd quartile	-0.62	-1.04, -0.21*	0.0034				
							4th quartile	-0.83	-1.28, -0.38*	0.0003				

Study	Outcome Category	Study Design	Sample Size	Exposure Metric	Outcome Assessed	Effect Measure	Unit of Measure	Effect Estimate	95% CI	P for Risk Estimates
							Per unit increment	-0.05	-0.08, -0.01*	0.0078
Ebisu and Bell, 2012	Developmental	Cohort	1,207,800	Air monitors	LBW	% change	Per IQR increment	5.7	2.7, 8.8	< 0.05
Heck et al., 2013	Developmental	Case-control	14,677	Air monitors (5 km)	Neuroblastoma	OR	Per IQR increment	1.08	0.71, 1.66	NR
				Air monitors (2.5 km)				0.67	0.29, 1.56	NR
Roberts et al., 2013	Developmental	Nested case-control	22,426	US EPA HAPs data (1990, 1996, 1999, 2002)	ASD (both sexes)	OR	1st quintile	REF		0.01#
							2nd quintile	1.3	0.9, 1.9	
							3rd quintile	1.6	1.1, 2.2	
							4th quintile	1.5	1.0, 2.2	
							5th quintile	1.7	1.1, 2.5	
					ASD (boys)	OR	1st quintile	REF		0.004#
							2nd quintile	1.4	0.9, 2.0	
							3rd quintile	1.6	1.1, 2.4	
							4th quintile	1.7	1.1, 2.6	
							5th quintile	1.9	1.2, 2.9	
					ASD (girls)	OR	1st quintile	REF		0.48#
							2nd quintile	1.1	0.5, 2.5	
							3rd quintile	1.2	0.5, 3.0	
							4th quintile	0.7	0.3, 2.1	
							5th quintile	0.7	0.2, 2.2	
Basu et al., 2014	Developmental	Cohort	646,296	Air monitors	LBW	% change in odds	Per IQR increment	1	0, 1	NR
					BW	Mean change (g)	Per IQR increment	-1	-2, -1	NR
Fuertes et al., 2014	Developmental	Meta-analysis	15,980	LUR modeled PM <sub>2.5</sub> nickel concentrations	Pneumonia	OR	Per ng/m <sup>3</sup>	0.84	0.67, 1.05	NR
				LUR modeled PM <sub>10</sub> nickel concentrations			Per 2 ng/m <sup>3</sup>	1.09	0.83, 1.43	NR
Laurent et al., 2014	Developmental	Cohort	960,945	CTM modeled PM <sub>2.5</sub> nickel concentrations	LBW	OR	Per IQR increment	1.009	1.003, 1.015	< 0.05

Study	Outcome Category	Study Design	Sample Size	Exposure Metric	Outcome Assessed	Effect Measure	Unit of Measure	Effect Estimate	95% CI	P for Risk Estimates		
				CTM modeled PM <sub>0.1</sub> nickel concentrations				1.009	1.004, 1.014	<0.05		
Manduca et al., 2014	Developmental	Case-control	60	Hair (neonatal)	Birth defects	NR	NA	NR	NR	NR		
			21		Premature births							
McDermott et al., 2014	Developmental	Cohort	9,920	Soil	LBW	OR	Per mg/kg increment	1	0.98, 1.02	NR		
Ni et al., 2014	Developmental	Cross-sectional	201	Umbilical cord blood	8-OHdG (DNA oxidative damage biomarker)	Mean change (ng/mL)	Per ng/mL	0.215	0.113, 0.317	< 0.001		
Zheng et al., 2014	Developmental	Case-control	179	Umbilical cord blood	Adverse pregnancy outcomes	Difference in medians (µg/L)	NA	-1.02*	NR	0.732		
Heck et al., 2015	Developmental	Case-control	30,704	Air monitors	Retinoblastoma	OR	Per IQR increment	1.48	1.08, 2.01	< 0.05		
Hu et al., 2015	Developmental	Cross-sectional	81	Maternal blood	Birth weight	Mean change (g)	NR	45.6	-17.2, 108.4	0.152		
				Cord blood				32.2	-19.8, 84.1	0.221		
Pedersen et al., 2016	Developmental	Meta-analysis	34,923	LUR modeled PM <sub>2.5</sub> nickel concentrations	LBW	OR	Per ng/m3	1.14 <sup>b</sup>	1.00, 1.29	NR		
								1.11 <sup>c</sup>	0.94, 1.31			
								1.1 <sup>d</sup>	0.91, 1.33			
				Per 2 ng/m3				1.29 <sup>b</sup>	0.96, 1.75	NR		
								1.14 <sup>c</sup>	0.90, 1.43			
								1.07 <sup>d</sup>	0.85, 1.35			
				LUR modeled PM <sub>2.5</sub> nickel concentrations			Birth weight	Mean change (g)	Per ng/m3	4 <sup>b</sup>	-15, 22	NR
										7 <sup>c</sup>	-13, 26	
										7 <sup>d</sup>	-50, 16	
				LUR modeled PM <sub>10</sub> nickel concentrations					Per 2 ng/m3	1 <sup>b</sup>	-22, 24	NR
-6 <sup>c</sup>	-33, 20											
7 <sup>d</sup>	-26, 39											

Study	Outcome Category	Study Design	Sample Size	Exposure Metric	Outcome Assessed	Effect Measure	Unit of Measure	Effect Estimate	95% CI	P for Risk Estimates	
				LUR modeled PM <sub>2.5</sub> nickel concentrations	Head circumference	Mean change (cm)	Per ng/m <sup>3</sup>	-0.6 <sup>b</sup>	-0.71, -0.49	NR	
				-0.49 <sup>c</sup>				-0.61, -0.36			
				-0.31 <sup>d</sup>				-0.44, -0.19			
				LUR modeled PM <sub>10</sub> nickel concentrations			Per 2 ng/m <sup>3</sup>	-0.46 <sup>b</sup>	-0.57, -0.36	NR	
								-0.34 <sup>c</sup>	-0.45, -0.22		
								-0.05 <sup>d</sup>	-0.20, 0.09		
Togawa et al., 2016	Developmental	Case-control	34,376	Employment (paternal)	Testicular germ cell tumors	OR	NR	1	0.96, 1.04	0.93	
				Employment (maternal)				1.09	0.91, 1.31	0.34	
				Employment (paternal)			None	REF		NR	
							Low	1.08	1.00, 1.18		
							High	1.03	0.85, 1.24		
				Employment (maternal)			None	REF		NR	
							Low	1	0.66, 1.51		
							High	1.27	0.66, 2.44		
Yan et al., 2016	Developmental	Case-control	452	Hair	Total NTD	OR	Low vs. high	0.53	0.34, 0.81	< 0.01	
								Anencephaly	0.5	0.27, 0.91	< 0.05
								Spina bifida	0.42	0.23, 0.76	< 0.01
								Encephalocele	0.82	0.32, 2.11	> 0.05

Notes:

\* Calculated; 95% CI was not reported in the study.

# P-value for trend test was reported.

8-OHdG = 8-Hydroxy-2'-Deoxyguanosine; ASD = Autism Spectrum Disorders; BMIC = Body Mass Index of Newborn Children; BW = Birth Weight; CI = Confidence Interval; CTM = Chemical Transport Models; DHEA-S = Dehydroepiandrosterone Sulfate; DNA = Deoxyribonucleic Acid; FSH = Follicle-Stimulating Hormone; HAPs = Hazardous Air Pollutants; IQR = Interquartile Range; LBW = Low Birth Weight; LH = Luteinizing Hormone; LUR = Land Use Regression; NA = Not Applicable; NR = Not Reported; NTD: Neural Tube Defects; OR = Odds Ratio; PCOS= Polycystic Ovary Syndrome; PI = Propidium Iodide; PM = Particulate Matter; POR = Prevalence Odds Ratio; PPB = Parts Per Billion; R = Correlation Coefficient; SA = Spontaneous Abortion; SGA = Small for Gestational Age; SHBG = Sex Hormone Binding Globulin; T = Testosterone; TSH = Thyroid Stimulating Hormone; US EPA = United States Environmental Protection Agency.

(a) 4th quartile result.

(b) Single-pollutant model.

(c) Two-pollutant model, adjusted for mass.

**Table 3 Risk-of-bias Criteria for Epidemiology Studies Evaluating Nickel Exposure and Reproductive and Developmental Outcomes**

	Key Criteria			Other RoB Criteria					
	Can we be confident in the exposure characterization?	Can we be confident in the outcome assessment?	Did the study design or analysis account for important confounding and modifying variables?	Was the study subject to selection bias?	Was the study subject to attrition bias?	Did the study employ appropriate statistical approaches?	Did the study report exposure levels?	Did the study assess the appropriate form of nickel?	Did the study assess the temporality of exposure and outcome?
<b>Definitely Low RoB criteria (++)</b>	<b>Co, CaCo, CrSe:</b> There is direct evidence that exposure was consistently assessed using well-established methods that directly measure exposure (e.g., measurement of Ni in blood, plasma, urine, semen)	<b>Co, CaCo, CrSe:</b> There is direct evidence that outcome was assessed using well-established methods (gold standard, e.g., physician verification), and outcome assessors were blinded to the exposure level <b>Co, CaCo:</b> Subjects had been followed for the same length of time in all study groups	<b>Co, CaCo, CrSe:</b> There is direct evidence that appropriate adjustments were made or considered for primary covariates and confounders (using valid and reliable measurements), and other exposures anticipated to bias results were not present or were adjusted for	<b>Co, CrSe, CaCo:</b> There is direct evidence that subjects (exposed vs unexposed, cases vs controls) were similar (e.g., recruited from the same eligible population, using the same inclusion and exclusion criteria), recruited within the same time frame, and had similar high participation/ response rates.	<b>CaCo, CrSe:</b> There is direct evidence that exclusion of subjects from analyses was adequately addressed, and reasons were documented when subjects were removed/excluded <b>Co:</b> Direct evidence that loss of subjects was adequately addressed and reasons were documented when subjects were removed	There is direct evidence that the study employed appropriate statistical methods (e.g., Cox models), and performed sensitivity analyses to inform the stability of findings, which yielded robust results	Reported exposure levels with units (e.g., mean/ median Ni levels) consistently and the quantified exposure contrast for effect estimates (e.g., per 1 ng/m <sup>3</sup> increase in Ni)	There is direct evidence that the study assessed appropriate exposure form (e.g., metal, soluble compounds, insoluble compounds) for a certain outcome	There is direct evidence that the exposure precedes the outcome, i.e., a temporal relationship between exposure and outcome can be established
<b>Probably low RoB criteria (+)</b>	<b>Co, CaCo, CrSe:</b> There is indirect evidence that exposure was consistently assessed using well-established methods that directly measure exposure (e.g., questionnaire or JEM) that have been validated	<b>Co, CaCo, CrSe:</b> There is indirect evidence that outcome was assessed using acceptable methods (e.g., medical records, cancer registry, blood sample, birth certificate), and outcome assessors were blinded to the	<b>Co, CaCo, CrSe:</b> There is indirect evidence that appropriate adjustments were made or considered for primary covariates and confounders (using valid and reliable measurements), and other exposures anticipated to	<b>Co, CrSe, CaCo:</b> There is indirect evidence that subjects were similar, recruited within the same time frame, and had similar high participation/ response rates, OR differences between groups would not appreciably bias results	<b>CaCo, CrSe:</b> There is indirect evidence that exclusion of subjects was adequately addressed, and reasons were documented when subjects were removed/excluded <b>Co:</b> Indirect evidence that loss of subjects was adequately addressed and reasons were		Reported exposure levels with units and the ordinal exposure contrast for effect estimates (e.g., high vs. median vs. low Ni levels)	There is indirect evidence that the study assessed appropriate exposure form for a certain outcome	There is indirect evidence that the exposure precedes the outcome

	Key Criteria			Other RoB Criteria					
	Can we be confident in the exposure characterization?	Can we be confident in the outcome assessment?	Did the study design or analysis account for important confounding and modifying variables?	Was the study subject to selection bias?	Was the study subject to attrition bias?	Did the study employ appropriate statistical approaches?	Did the study report exposure levels?	Did the study assess the appropriate form of nickel?	Did the study assess the temporality of exposure and outcome?
		exposure level <b>Co, CaCo:</b> Subjects had been followed for the same length of time in all study groups	bias results were not present or were adjusted for		documented when subjects were removed				
<b>Probably high RoB criteria (-)</b>	<b>Co, CaCo, CrSe:</b> There is indirect evidence that the exposure was assessed using poorly validated methods that directly measure exposure, OR direct evidence that exposure was assessed using indirect measures that have not been validated (e.g., air/soil measurement, JEM or self-report without validation, record "NR")	<b>Co, CaCo, CrSe:</b> There is indirect evidence that outcome was assessed using insensitive instruments (e.g., questionnaire without validation) OR insufficient information re: how cases were identified (record "NR"), and outcome assessors were likely not blinded to the exposure level, OR insufficient information re: blinding (record "NR") <b>Co:</b> The length of follow up differed by study group	<b>Co, CaCo, CrSe:</b> There is indirect evidence that primary covariates, known confounders, or co-exposures were not appropriately adjusted, OR using measurements of unknown validity, OR insufficient information re: the measurement techniques used (record "NR") or co-exposures (high exposures to other chemicals would be anticipated in occupational studies, record "NR")	<b>Co, CrSe, CaCo:</b> There is evidence (indirect for Co, CrSe, but direct for CaCo) that subjects were not similar, recruited within very different time frames, or had the very different participation/ response rates, OR insufficient information re: the comparison group including a different rate of non-response without an explanation (record "NR")	<b>CaCo, CrSe:</b> There is indirect evidence that exclusion of subjects from analyses was not adequately addressed OR insufficient information re: why subjects were removed ("NR") <b>Co:</b> Indirect evidence that loss of subjects (i.e., incomplete outcome data) was unacceptably large and not addressed, OR there is insufficient information re: numbers of subjects lost to follow-up (record "NR")	There is indirect evidence that the study did not use appropriate statistical methods, or did not assess underlying model assumptions, e.g., PH assumption (NR), or did not perform or report results from sensitivity analyses (NR).	Did not report exposure levels, units, or exposure contrasts (NR)	There is indirect evidence that the study assessed inappropriate exposure form for a certain outcome, OR insufficient information re: the nickel form (report "NR")	There is indirect evidence that the temporal relationship between exposure and outcome cannot be established

	Key Criteria			Other RoB Criteria					
	Can we be confident in the exposure characterization?	Can we be confident in the outcome assessment?	Did the study design or analysis account for important confounding and modifying variables?	Was the study subject to selection bias?	Was the study subject to attrition bias?	Did the study employ appropriate statistical approaches?	Did the study report exposure levels?	Did the study assess the appropriate form of nickel?	Did the study assess the temporality of exposure and outcome?
Definitely high RoB criteria (--)	<p><b>Co, CaCo, CrSe:</b> There is direct evidence that exposure was assessed using methods with poor validity, OR evidence of exposure misclassification (<i>e.g.</i>, differential recall of self-reported exposure in CaCo)</p>	<p><b>Co, CaCo, CrSe:</b> There is direct evidence that outcome was assessed using insensitive instrument, OR there is direct evidence that outcome assessors were not blinded to the exposure level</p> <p><b>Co:</b> The length of follow up differed by study group</p>	<p><b>Co, CaCo, CrSe:</b> There is direct evidence that primary covariates, known confounders, or co-exposures were not appropriately adjusted, OR used nonvalid measurements</p>	<p><b>Co, CrSe, CaCo:</b> There is direct evidence that subjects (<i>e.g.</i>, cases vs. controls) were not similar, recruited within very different time frames, or had very different/low response rates.</p>	<p><b>CaCo, CrSe:</b> There is direct evidence that exclusion of subjects was not adequately addressed (<i>e.g.</i>, reason of exclusion likely to be related to true outcome)</p> <p><b>Co:</b> Direct evidence that loss of subjects was unacceptably large and not addressed</p>	<p>There is direct evidence that the study did not employ appropriate statistical methods (underlying assumption was violated), or sensitivity analyses indicated unstable findings</p>		<p>There is direct evidence that the study assessed inappropriate exposure form for a certain outcome</p>	<p>There is direct evidence that the temporal relationship between exposure and outcome cannot be established</p>

Notes:

CaCo = Case-Control; Co = Cohort; CrSe = Cross-Sectional; JEM = Job-Exposure Matrix; Ni = Nickel; NR = Not Reported; RoB = Risk of Bias

**Table 4 Risk-of-bias Analysis of Epidemiology Studies Evaluating Nickel Exposure and Reproductive and Developmental Outcomes**

Study	Key Criteria			Other RoB Criteria					
	Can we be confident in the exposure characterization?	Can we be confident in the outcome assessment?	Did the study design or analysis account for important confounding and modifying variables?	Was the study subject to selection bias?	Was the study subject to attrition bias?	Did the study employ appropriate statistical approaches?	Did the study report exposure levels?	Did the study assess the appropriate form of nickel?	Did the study assess the temporality of exposure and outcome?
Bloom et al., 2011	++	--	-	+	++	NR	++	NR	++
Zheng et al., 2015	++	+	--	--	++	NR	++	NR	--
Maduray et al., 2017	++	+	--	NR	++	--	++	NR	--
Danadevi et al., 2003	++	+	--	+	++	NR	++	NR	--
Slivkova et al., 2009	++	+	--	+	++	--	++	NR	--
Zeng et al., 2013	++	+	-	+	++	NR	++	NR	--
Sancini et al., 2014	++	+	--	+	++	NR	++	NR	--
Skalnaya et al., 2015	++	+	--	+	++	--	++	NR	--
Zafar et al., 2015	++	+	--	+	++	--	++	NR	--
Zeng et al., 2015	++	+	-	+	++	NR	++	NR	--
Wang et al., 2016	++	+	--	+	++	NR	++	NR	--
Zhou et al., 2016	++	+	-	+	++	NR	++	NR	--
Chashschin et al., 1994	++	+	--	+	++	NR	NR	++	--
Odland et al., 1999	++	+	--	+	++	NR	++	NR	--
Odland et al., 2004	++	+	--	+	++	NR	++	NR	--
Friel et al., 2005	++	+	--	+	++	--	++	NR	--
Vaktskjold et al., 2006	++	+	--	+	++	NR	NR	++	++
Windham et al., 2006	NR	+	-	-	++	NR	++	NR	--
Vaktskjold et al., 2007	++	+	-	+	++	NR	NR	++	++
Vaktskjold et al., 2008a	++	--	-	+	++	NR	NR	++	++
Vaktskjold et al., 2008b	++	+	-	+	++	NR	NR	++	++
Bell et al., 2010	NR	+	++	+	++	NR	++	++	++
Kalkbrenner et al., 2010	NR	+	-	+	++	++	++	++	++
Huang et al., 2011	NR	++	NR	+	++	NR	NR	NR	--

Study	Key Criteria			Other RoB Criteria					
	Can we be confident in the exposure characterization?	Can we be confident in the outcome assessment?	Did the study design or analysis account for important confounding and modifying variables?	Was the study subject to selection bias?	Was the study subject to attrition bias?	Did the study employ appropriate statistical approaches?	Did the study report exposure levels?	Did the study assess the appropriate form of nickel?	Did the study assess the temporality of exposure and outcome?
Zheng et al., 2012	NR	+	--	+	++	NR	++	NR	--
Ebisu and Bell, 2012	NR	+	++	+	++	++	++	++	++
Heck et al., 2013	NR	+	-	-	++	NR	++	++	++
Roberts et al., 2013	NR	--	-	+	++	NR	++	++	++
Basu et al., 2014	NR	+	-	+	++	++	++	++	++
Fuertes et al., 2014	--	--	-	+	++	++	NR	++	++
Laurent et al., 2014	NR	+	-	+	++	++	NR	++	++
Manduca et al., 2014	++	+	--	NR	++	--	NR	NR	--
McDermott et al., 2014	NR	+	-	+	++	NR	++	NR	++
Ni et al., 2014	++	+	-	+	++	NR	NR	NR	--
Zheng et al., 2014	++	+	--	+	++	--	++	NR	--
Heck et al., 2015	NR	+	-	-	++	++	++	++	++
Hu et al., 2015	++	+	--	+	++	NR	NR	NR	--
Pedersen et al., 2016	NR	--	-	+	++	++	++	++	++
Togawa et al., 2016	NR	+	--	+	++	++	NR	NR	++
Yan et al., 2016	++	+	-	+	++	NR	++	NR	++

Notes:

NR = Not Reported; RoB = Risk of Bias