Comments on the 2015 DART Prioritization Listing of Nickel (CAS #7440-02-0) for Consideration as a Reproductive or Developmental Toxicant Under Proposition 65

Submitted by Julie E. Goodman, Ph.D., DABT, ACE, ATS of Gradient
On Behalf of the Nickel Producers Environmental Research Association (NiPERA)

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GRADIENT
www.gradientcorp.com
20 University Road
Cambridge, MA 02138
617-395-5000

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1 Introduction

The California Office of Environmental Health Hazard Assessment (CalOEHHA) proposed nickel (CAS[1] #7440-02-0) as a chemical for review by the Developmental and Reproductive Toxicant Identification Committee (DARTIC) under Proposition 65, using the prioritization process endorsed by DARTIC and adopted by CalOEHHA in 2004 (CalOEHHA, 2004; 2015). CalOEHHA requested public comment regarding whether nickel should proceed to the next stage of the listing process, which involves hazard identification development by CalOEHHA. DARTIC will provide consultation to CalOEHHA regarding this next phase at its November 9, 2015, meeting.

CalOEHHA recently performed a preliminary epidemiology screen and toxicity evaluation on several chemicals identified in 2007 as having relevant but not sufficient human data regarding reproductive and developmental effects at that time. Based on a review of study abstracts, "two or more analytical studies of adequate quality" reporting a significant association are required to pass the epidemiology screen CalOEHHA (2015). CalOEHHA identified what it considered to be three such studies reporting a statistically significant association between nickel and adverse developmental or reproductive outcomes, and four reporting similar associations that were not of adequate quality.

We conducted an independent literature search and identified a total of 21 studies, including the three key epidemiology studies and others identified by CalOEHHA (Tables 1, 2, and Appendix A). Based on a critical review of this literature, including an evaluation of study quality and risk of bias, we conclude the following:

1. The three studies identified by CalOEHHA are not of adequate quality and do not support prioritization of nickel;
2. Other studies CalOEHHA identified with statistically significant results also are not of adequate quality;
3. Overall, the epidemiology evidence does not support an association between nickel exposure and adverse developmental or reproductive outcomes in humans;
4. Nickel in metallic form (CAS #7440-02-0) should not be listed for consideration; and
5. When considered in light of epidemiology findings, animal bioassays do not indicate that nickel should be prioritized.

The bases for these conclusions are described in the following sections.

[1] Chemical Abstracts Service Registry Number (CAS RN).

2 Bell *et al*. (2010), Ebisu and Bell (2012), and Guo *et al*. (2010) Are Not "Analytical Epidemiology Studies of Adequate Quality" and Do Not Support Prioritization of Nickel

In its prioritization document for Proposition 65 DARTIC consideration, CalOEHHA (2015) indicated that it requires "two or more analytical studies of adequate quality reporting an association between nickel exposure and increased risk of adverse developmental or reproductive outcomes" for nickel to pass the epidemiology screening requirements for inclusion on the prioritization list for DARTIC review. CalOEHHA (2004; 2015) did not provide specific criteria to define "adequate quality," but stated in its process for prioritizing chemicals for consideration under Proposition 65 (CalOEHHA, 2004) that various factors are considered in weighing the epidemiology evidence, including "type of study (*e.g.*, case-control), study population, exposure situation, endpoint (*e.g.*, tumor type, developmental effect), dose-response, possible roles of bias and confounding, and overall study quality." CalOEHHA (2015) identified seven studies as reporting statistically significant increased risk of adverse developmental or reproductive outcomes associated with nickel exposure, and determined that three – Bell *et al*. (2010), Ebisu and Bell (2012), and Guo *et al*. (2010) (see Tables 1, 2, and A1) – were analytical studies of "adequate quality" based on a review of study abstracts. As discussed below and in further detail in Section 4, this is not the case.

Bell *et al*. (2010) reported that prenatal exposure to nickel in fine particulate matter ($PM_{2.5}$) is associated with an 11% increased risk of low birth weight in a US cohort. This study relied on centrally located air monitors to provide source exposure estimates of $PM_{2.5}$ at the residential county level at the time of birth (Tables 1 and A1). Such exposure measurements do not reflect personal exposures or personal activity patterns (*e.g.*, occupational exposures), proximity to air monitors, or the possibility for relocation during pregnancy, and therefore do not provide accurate individual exposure estimates. In addition, gestational exposure was estimated based on the last menstrual period (LMP) reported on the birth certificate; LMP is an approximate date and can result in further misclassification of gestational exposure. Finally, there is the potential for confounding due to a lack of pertinent information on birth certificates that may be associated with both PM and low birth weight (*e.g.*, maternal weight or maternal socioeconomic status) and from co-exposure to other constituents associated with this outcome.

Ebisu and Bell (2012) conducted a follow-up to the Bell *et al.* (2010) study with an expanded cohort that included women and their children in the mid-Atlantic coast and northeast US. These investigators found an association between nickel in $PM_{2.5}$ and low birth weight. One improvement of this study over the earlier study is that the authors conducted bi-pollutant analyses to account for potential confounding by other PM constituents. They found that the risk estimate for nickel attenuated considerably when adjusted for elemental carbon, indicating that elemental carbon was a confounder. However, this study still contained the limitations of the original Bell *et al.* (2010) study (*e.g.*, extensive exposure measurement error), in addition to the fact that these bi-pollutant models evaluated confounding by other PM constituents one at a time.

The third study cited by CalOEHHA as having adequate quality is that by Guo *et al*. (2010), a cross-sectional study of mothers and children in China living in the electronic waste recycling town of Guiyu

and in a control area nearby. The authors found that the median placental nickel concentrations were lower in women from the e-recycling area (Guiyu: 7.64 ng/g wt) than from the control area (14.30 ng/g wt), suggesting that the high nickel exposure was from sources other than e-waste. Mothers living in Guiyu and in the control area also differed significantly with regard to maternal age and education. The authors found a negative correlation between placental nickel obtained after delivery and gestational age. However, the crude statistical approach they used does not allow adjustment for confounders, and the observed correlation between nickel concentrations in the placenta and gestational age could be explained by the differences in maternal age and education. These methodological limitations and apparent biases severely undermine the validity of the study findings.

In conclusion, the three studies identified by CalOEHHA (2015) have considerable methodological limitations and/or apparent biases (as discussed above and in Section 4), and therefore should not be considered of "adequate quality" or used as the primary support for prioritization for DARTIC review.

3 As Implied by CalOEHHA, Huang *et al*. (2011), Vaktskjold *et al*. (2004a), Danadevi *et al*. (2003), and Chashschin *et al*. (1994) Reported Statistically Significant Associations But Are Not of Adequate Quality

Based on a review of study abstracts, CalOEHHA (2015) identified four studies that reported a statistically significant increased risk of adverse developmental or reproductive outcomes (Huang *et al*., 2011; Vaktskjold *et al*., 2004a; Danadevi *et al*., 2003; Chashschin *et al*., 1994; see Tables 1, 2, and A1). However, as CalOEHHA (2015) alluded, these four studies are not of adequate quality and cannot be used to justify listing nickel as a priority chemical for DARTIC review.

A close review of the studies revealed that two of the four (Huang *et al*., 2011; Vaktskjold *et al*., 2004a) did not investigate nickel exposure and reproductive or developmental outcomes. Huang *et al*. (2011) described a model built to analyze the association between trace elements in cultivated soil and the prevalence of neural tube defects. This is a model building exercise and the authors' main objective was to determine the normal ranges of trace elements in the soil. Limitations of this study include a lack of information regarding the number of neural tube defect cases, a lack of population characteristics, and a lack of quantitative information regarding statistical significance and prevalence.

Vaktskjold *et al*. (2004a) described a cohort of women in Moncegorsk, Russia. The authors considered pregnancy history, pertinent medical history, distribution of occupations, and the proportion of women potentially exposed to compounds of nickel and other metals. This cohort was evaluated in several other studies reviewed here (Vaktskjold *et al*., 2006, 2007, 2008a, b; see Section 4). Vaktskjold *et al*. (2004a) did not assess the association between nickel exposure and any reproductive or developmental outcome.

Danadevi *et al*. (2003) and Chashschin *et al*. (1994) suffer from several limitations, including relatively small sample sizes, simplistic statistical analyses providing measures of correlation rather than measures of association, uncontrolled exposures to other metals, and unclear presentations of results. Based on these limitations, we agree with CalOEHHA (2015) that these studies are not of adequate quality and thus do not support the prioritization of nickel for review.

4 The Epidemiology Evidence As a Whole Does Not Support an Association Between Nickel Exposure and Adverse Reproductive Outcomes in Humans

CalOEHHA (2015) identified a total of 20 studies based on a review of abstracts as investigating an association between nickel exposure and adverse reproductive or developmental outcomes. Our independent literature search identified one additional study not included in CalOEHHA's list (Vaktskjold *et al*., 2004b). Of the twenty-one studies reviewed, twelve reported no statistically significant associations between nickel exposure and adverse reproductive or developmental outcomes (Bloom *et al*., 2011; Vaktskjold *et al*., 2006, 2007, 2008a, b; Jelnes and Knudsen, 1988; McDermott *et al*., 2014; Pietrzyk *et al*., 1994; Odland *et al*., 1999, 2004; Windham *et al*., 2006; Zheng *et al*., 2014), five reported statistically significant associations between nickel exposure and measured outcomes (Bell *et al*., 2010; Ebisu and Bell, 2012; Guo *et al*., 2010; Danadevi *et al*., 2003; Chashschin *et al*., 1994), three did not evaluate an association (Vaktskjold *et al*., 2004a, 2004b; Huang *et al*., 2011), and one was not in English (Talykova, 2009).

Because no specific criteria are provided by CalOEHHA (2015) to evaluate study quality, we developed criteria to evaluate the validity of results of these epidemiology studies based on those developed by the US Environmental Protection Agency (US EPA, 2014, 2015) and others (Goodman *et al*., 2015a,,b; Kerper *et al*., 2014). High-quality studies have the following characteristics:

- More robust study designs, such as prospective cohort and nested case-control studies;
- A larger sample size;
- A study population that is less limited by selection bias, such as the general population;
- Clear evidence of a temporal relationship;
- Personal exposure measurements, such as blood, urine, or placental nickel levels;
- Verified methods for outcome ascertainment, such as birth certificates and medical records;
- Adequate consideration of potential confounders; and
- Appropriate statistical approach, such as linear or logistic regression.

We conducted a risk-of-bias analysis based on study quality characteristics that may have impacted the validity of the study findings, including study design, study size, whether appropriate statistical approaches were used to assess potential confounding relationships between the exposure and the outcome of interest, whether the exposure was a personal measurement, whether the outcome was ascertained in an objective manner, whether there was clear evidence of temporality, and whether the analyses adjusted for potential confounders (*e.g.*, maternal age, parity, socioeconomic status). Because these study quality characteristics likely had different impacts on the results, we divided them into three tiers (Tier I, II, or III). Our risk-of-bias analysis strategy is presented in Figure 1 and described in detail below.

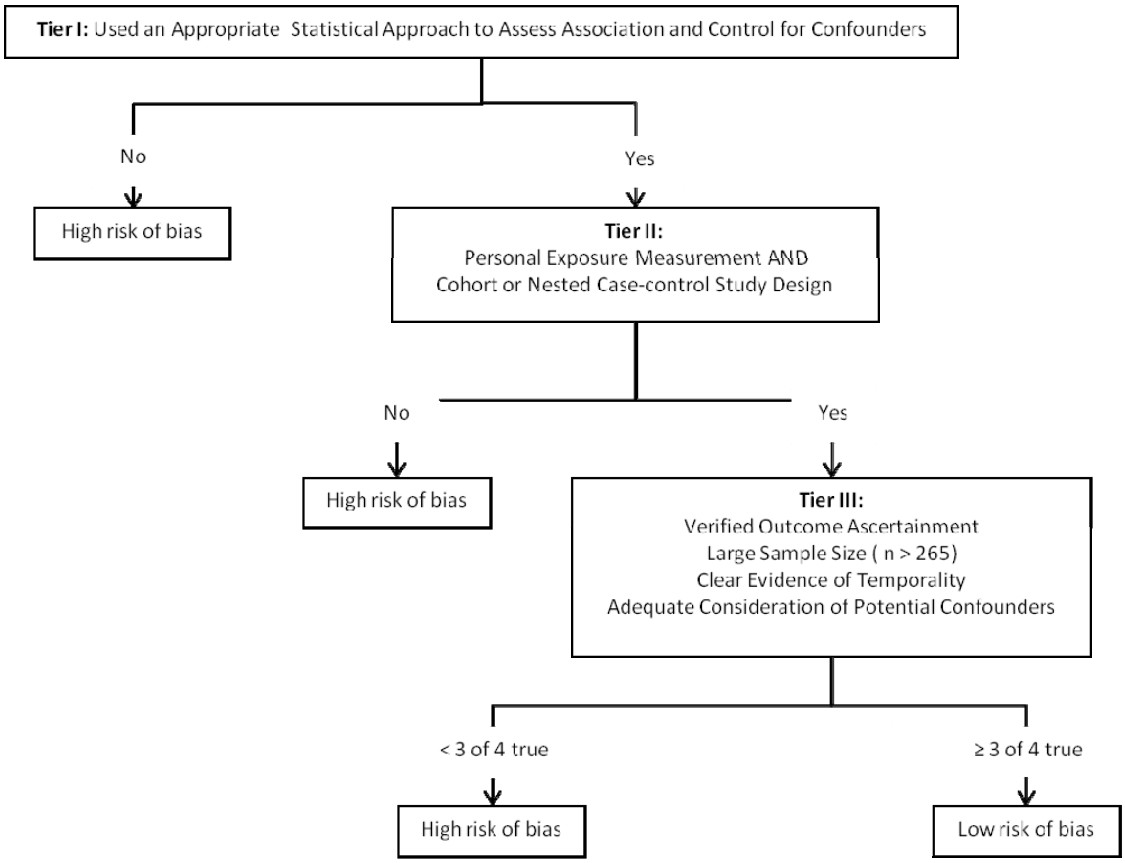

Figure 1 Risk-of-bias Analysis

Tier I: Appropriate Statistical Approach

We first considered whether the authors used appropriate statistical approaches to assess potential confounders. For example, simple correlation analyses do not incorporate proper statistical adjustments to assess potential confounders, have a high risk of bias, and are of lower quality.

Tier II: Exposure Measurement and Study Design

We considered two Tier II criteria:

- Exposure Measurement: If a study used personal biological samples, such as blood, urine, and placenta, to measure nickel exposure, the exposure measurement error is likely minimized and we considered this criterion met. If a study relied on central site air monitoring or soil samples from the residential community/area to estimate exposures, substantial exposure measurement error is likely because these measurements were obtained at area level. These studies did not meet the exposure measurement criterion.
- Study Design: If a study employed a robust study design (*i.e.*, cohort, nested case-control), we considered this criterion met. Case-control studies are not robust because they are generally limited by selection bias and recall bias. Cross-sectional studies are also less robust because the exposure and outcome are assessed at a single time point, and no temporal relationship can be established between them.

If a study meets the Tier I and both of the two Tier II criteria, it has a low risk of bias and is considered to be of higher quality. Otherwise, it has a high risk of bias and is of lower quality.

Tier III: Outcome Ascertainment, Sample Size, Temporality, and Adjustment of Potential Confounders

We considered four Tier III criteria:

- Outcome Ascertainment: If a study ascertained the outcome of interest based on verified or well-documented methods, such as birth certificates, ejaculate testing, physician verification, or medical records, we considered this criterion met. Outcomes ascertained through questionnaire or self-report may introduce both random and systematic errors, so studies using these methods did not meet this criterion.
- Sample Size: Smaller studies are less precise and are more prone to chance findings than larger studies. However, none of the epidemiology studies described *a priori* estimates of study power. Therefore, we defined the cut-off based on the median sample size of the reviewed studies. If a study had a sample size of 265 subjects or fewer, it did not meet this criterion.
- Temporality: If a study adequately and logically assessed the temporal relationship between nickel exposure and the outcome of interest, we considered this criterion met. If a study did not provide clear evidence that the exposure preceded the outcome, the study did not meet this criterion. For example, if the exposure (soil) was measured after the outcome of interest (*e.g.*, birth weight), temporality was not properly established.
- Adjustment of Potential Confounders: We determined whether each study accounted for potential confounders in each of five categories – maternal age, parity, smoking, socioeconomic status (SES) factors, and health – as failure to control for any of these categories can bias study results. It should be noted that some of these categories are not relevant to certain reproductive outcomes (for example, maternal age and parity are not related to semen quality). In these cases, we considered those categories as "not applicable" for studies evaluating that paritcular outcome. For the category of SES factors, we required a study to measure and control for at least one SES factor, such as education, income, or employment. For the category of health, we required a study to measure and control for at least one health-related factor that could be associated with nickel and the exposure of interest, such as maternal medical history of the outcome of interest, body mass index (BMI), or alcohol consumption during pregnancy. If a study controlled for all five confounder categories, it met this criterion. In cases where some potential confounders were considered "not applicable," studies needed to control for all applicable confounders to meet this criterion.

Each of these Tier III criteria is likely to have a smaller impact on a study's risk of bias than using an inappropriate statistical approach (Tier I) or less robust study designs (Tier II). Thus, a study has a low risk of bias and is of higher quality if it met all of the criteria in Tiers I and II, and also met three or more Tier III criteria (*i.e.*, all five confounders controlled for in addition to at least two of three of the other Tier III criteria); if it met less than three of the four Tier III criteria, we considered it to have a high risk of bias and be of lower quality.

The results of our risk-of-bias analysis are presented in Table 3. Overall, the majority of the epidemiology studies (16 of 18) of nickel and reproductive and developmental outcomes had mixed results and a high risk of bias, and were of low quality, including four studies that reported a positive dose-response relationship between nickel exposure and the assessed outcome. In general, most of these

studies did not employ an appropriate statistical approach to assess potential confounding, utilized area-level exposure measurements and less robust study designs, had small sample sizes, and were not able to clearly assess the temporal relationship between the exposure and the outcome of interest, placing them at a high risk of bias; therefore, they were considered to be lower quality studies. In contrast, two studies had a lower risk of bias and were of higher quality compared to other studies (Vaktskjold *et al*., 2007, 2008a). Vaktskjold *et al*. (2007, 2008a) reported no association between nickel exposure and the developmental effects evaluated. These studies employed appropriate statistical approaches to assess potential confounding, assessed exposure using personal measurements, and adjusted for key potential confounders. As a whole, the available epidemiology studies do not support listing nickel as a priority substance for DARTIC review.

5 Nickel in Metallic Form (CAS #7440-02-0) Should Not Be Listed for Consideration

CAS #7440-02-0 is listed as a priority chemical for DARTIC review (CalOEHHA, 2015). This CAS Registry Number is specific to nickel metal and does not include other forms of nickel (*i.e.*, soluble and insoluble). In epidemiology studies, measurements of individual exposures to nickel using biological samples do not differentiate nickel forms. Still, Bell *et al*. (2010) and Ebisu and Bell (2012), two of the three key studies identified by DARTIC, could not have evaluated exposure to nickel metal because nickel oxides and sulfates are the predominant forms in air pollution. Also, nickel metal is not expected to be present in food, soil, or dust, indicating that it was not likely the main source of exposure in the other key study by Guo *et al*. (2010), who found higher exposures in the "non-exposed" population. Setting aside the arguments above regarding the low quality of these studies, these exposure considerations indicate that the prioritization listing for DARTIC review should not include nickel metal (CAS #7440-02-0).

6 When Considered in Light of Epidemiology Findings, Animal Bioassays Do Not Indicate that Nickel Should Be Prioritized

The worker-mother population from the Moncegorsk, Russia, cohort (Vaktskjold *et al*., 2004a, 2006, 2007, 2008a, 2008b) has the highest human exposures in the epidemiology studies we reviewed (urine nickel concentration ≥ 70 µg/L; this roughly corresponds to ≥ 160 µg/m^3 water-soluble nickel). For context, the levels at which adverse effects have been observed in rats orally exposed to soluble nickel compounds roughly correspond to a urinary concentration of 2,400 µg Ni/L (Rush, 2005). None of these studies reported associations between water-soluble nickel and adverse reproductive or developmental effects. In general, soluble nickel compounds are considered more toxic than the less-soluble compounds (ATSDR, 2005). Studies of animals exposed to certain soluble forms of nickel (*e.g.*, nickel sulfate) provide consistent evidence of certain developmental effects at very high exposure levels (*e.g.*, ≥ 2.2 mg Ni/kg/day) (*e.g.*, Springborn Laboratories, Inc., 2000a,b). Because the studies with the highest human exposures to water-soluble nickel do not indicate a reproductive or developmental hazard, this suggests that the mode of action for nickel toxicity observed in animals at high exposures may not be relevant to humans, and nickel exposure levels in animals may not be achievable in humans. This calls into question listing nickel for prioritization for review by DARTIC.

7 Conclusions

Overall, the epidemiology evidence does not support an association between nickel exposure and adverse reproductive or developmental outcomes in humans. The quality of the three studies identified by CalOEHHA (2015) as showing a statistical association is not sufficient, and therefore, these studies do not provide support for prioritization for DARTIC review. In addition, CAS #7440-02-0 should not be listed for consideration because metallic nickel represents a minor contributor to the nickel exposure in California. While animal studies indicate the potential for certain reproductive and developmental effects after high exposures (compared to humans) to soluble nickel compounds, these results are not supported by high-quality epidemiology studies of women occupationally exposed to high levels (compared to other women) of water-soluble nickel forms, which are the most bioavailable forms of nickel. These results suggest that the mode of action for nickel toxicity observed in animals at high exposures may not be relevant to humans. Taken together, the results indicate that nickel in metallic form certainly should not be listed for prioritization; nor should other forms of nickel.

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Tables

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

Study	Study Design	Study Population		Temporality	Exposure Assessment		Outcome Ascertainment	Potential Confounders Considered	Statistical Analysis		
		Selection Bias	Sample Size		Personal Measurement	Metric Used			Statistical Approach	Dose-Response Assessed	Dose-Response Relationship with Ni
Bell *et al.* , 2010	Cohort	Population-based	76,788	Yes	No	County-wide exposure estimates *via* ambient air monitors	Birth certificate	Yes	% Change	Yes	Yes
Ebisu and Bell, 2012	Cohort	Population-based	1,207,800	Yes	No	County-wide exposure estimates *via* ambient air monitors	Birth certificate	Yes	% Change	Yes	Yes
Huang *et al.* , 2011	Cohort	High risk	NR	No	No	Mixed village soil sample	Physician verification	NR	Prevalence	Yes	Yes
Bloom *et al.* , 2011	Cohort	Population-based	99	Yes	Yes	Whole blood	Home pregnancy test	Yes	% Change	Yes	No
Danadevi *et al.* , 2003	Case-control	High risk, Occupation	114	No	Yes	Whole blood	Ejaculate	NA	r	No	NA
McDermott *et al.* , 2014	Cohort	Minority	9,920	No	No	Soil concentrations at residence, neighborhood	Birth certificate	Yes	OR	Yes	No
Guo *et al.* , 2010	Cross-sectional	High risk	220	Yes	Yes	Placenta	Medical records	NA	r	No	NA
Chashschin *et al.* , 1994	Cross-sectional	High risk, Occupation	698	No	Yes	Urine, 24 hour	Medical records	Yes	POR	No	NA
Jelnes and Knudsen, 1988	Case-control	High risk, Occupation	145	No	Yes	Blood Urine	Ejaculate	No	NR	No	NA
Pietrzyk *et al.* , 1994	Case-control	Population-based	178	NR	Yes	Pubic and head hair	NR	No	F	NR	NR
Odland *et al.* , 1999	Cross-sectional	High risk, Occupation	265	No	Yes	Urine	Medical records	No	% Change	Yes	No
Odland *et al.* , 2004	Cross-sectional	High risk, Occupation	262	No	Yes	Blood Urine Placenta	Medical records	No	% Change	Yes	No
Zheng *et al.,* 2014	Case-control	Population-based	179	No	Yes	Umbilical cord blood	Medical records	No	OR	No	NA
Vaktskjold *et al.* , 2006	Nested Case-control	High risk, Occupation	23,141	No	Yes	Background, low, high	Medical records	No	OR	Yes	No
Vaktskjold *et al.* , 2007	Nested Case-control	High risk, Occupation	22,836	Yes	Yes	Background, low, high	Medical records	Yes	OR	Yes	No
Vaktskjold *et al.* , 2008a	Nested Case-control	High risk, Occupation	22,965	No	Yes	Background, low, high	Medical records	Yes	OR	Yes	No
Vaktskjold *et al.* , 2008b	Case-control	High risk, Occupation	1,875	No	Yes	Background, low, high	Medical records Self-report	Yes	OR	Yes	No
Windham *et al.* , 2006	Case-control	Population-based	941	No	No	1996 US EPA HAPs data	Medical records	High	OR	Yes	Yes

Notes:

F = F-statistic; HAP = Hazardous Air Pollutant; NA = Not Applicable; Ni = Nickel; NR = Not Reported; OR = Odds Ratio; POR = Prevalence Odds Ratio; r = Correlation Coefficient; US EPA = United States Environmental Protection Agency.

See Section 4 for more detail on quality criteria.

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

Study	Study Design	Sample Size	Exposure Metric	Outcome Assessed	Effect Measure	Unit of Measure	Effect Estimate	95% CI	P for Risk Estimates
Bell *et al* ., 2010	Cohort	76,788	Air monitors	LBW	% change in odds	per IQR increment	11	3, 19	NR
Ebisu and Bell, 2012	Cohort	1,207,800	Air monitors	LBW	% change in odds	per IQR increment	5.7	2.7, 8.8	< 0.05
Huang *et al* ., 2011	Cohort	NR	Soil	Neural tube defects	prevalence	Tertile (Low, Medium, High)	Unclear		
Bloom *et al* ., 2011	Cohort	99	Blood serum	Pregnancy	% change in odds	per IQR increment	-8.6		0.79
Danadevi *et al.* , 2003	Cross-sectional	114	Blood serum	Sperm count	r	NA	-0.352		0.067
				Rapid linear progressive motility			-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
McDermott *et al.* , 2014	Cohort	9,920	Soil	LBW	OR	Low *vs.* normal BW	1	0.98, 1.02	
Guo *et al* ., 2010	Cross-sectional	220	Placenta	Birth length	r	NA	-0.002		0.973
				Birth weight			-0.041		0.552
				Gestational age			-0.161		0.017
Chashschin *et al.,* 1994	Cross-sectional	698	Urine (24h)	All kinds of defects	pOR	NR	2.9		NR
				Cardiovascular system defects			6.1		NR
				Musculoskeletal defects			1.9		NR
Jelnes and Knudsen, 1988	Cross-sectional	145	Blood Urine	Semen quality	NR	NR	NR		NR
Pietrzyk *et al.* , 1994	Case-control	178	Pubic and head hair	Prematurity SGA	F	NR	NR		NR
Odland *et al.* , 1999	Cross-sectional	265	Maternal Urine	BW	Weight change	per gram	-1	-6, 5	> 0.05
				BMIC			0	-0.03, 0.004	> 0.05
Odland *et al.* , 2004	Cross-sectional	262	Blood Urine	BW	Weight change	per gram	-1510	-3191, 170	> 0.05
				BMIC			-2.73	-7.49, 2.02	> 0.05
Zheng *et al.* , 2014	Case-control	179	Umbilical cord blood	Adverse pregnancy outcomes	OR	Quartiles	NR		NR
Vaktskjold *et al.* , 2006	Nested Case-control	23,141	Employment, urine, air	Genital malformations	OR	Tertile (Background, Low, High)	0.81	0.52, 1.26	NR
Vaktskjold *et al.* , 2007	Nested Case-control	22,836	Employment, urine, air	SGA	OR	Tertile (Background, Low, High)	0.84	0.75, 0.93	NR
Vaktskjold *et al.* , 2008a	Nested Case-control	22,965	Employment, urine, air	Musculoskeletal defects	OR	Tertile (Background, Low, High)	0.96	0.76, 1.21	NR
Vaktskjold *et al.* , 2008b	Case-control	1,875	Employment, urine, air	SA (Questionnaire)	OR	Tertile (Background, Low, High)	1.14	0.95, 1.37	NR
		5,045		SA (Birth Registry)			0.87	0.72, 1.06	NR
Windham *et al.* , 2006	Case-control	941	1996 US EPA HAPS data	ASD	OR	Quartiles	1.46[a]	1.04, 2.06	NR

Notes:

(a) 4th quartile result.

ASD = Autism Spectrum Disorders; BMIC = Body Mass Index of Newborn Children; BW = Birth Weight; CI = Confidence Interval; F = F-Statistic; HAPS = Hazardous Air Pollutants; IQR = Interquartile Range; LBW = Low Birth Weight; NA = Not Applicable; NR = Not Reported; OR = Odds Ratio; pOR = Prevalence Odds Ratio; r = Correlation Coefficient; SA = Spontaneous Abortion; SGA = Small for Gestational Age.

Table 3 Risk-of-bias Analysis of Epidemiology Studies Evaluating Nickel Exposure and Reproductive and Developmental Effects[a]

Study	Tier I	Tier II		Tier III								Risk of Bias[c]
							Adjustment for:					
	Appropriate Statistical Approach to Assess Confounding	Personal Measurements	Cohort or Nested Case-Control Study Design	Verified Outcome Ascertainment	Large Sample Size	Temporality Assessment	Maternal Age	Parity	Smoking	SES	Health[b]	
Bell *et al.* , 2010	√	X	√	√	√	√	√	√	√	√	√	High
Ebisu and Bell, 2012	√	X	√	√	√	√	√	√	√	√	√	High
Huang *et al.* , 2011	X	X	√	√	NR	NR	NR	NR	NR	NR	NR	High
Bloom *et al.* , 2011	√	√	√	X	X	√	√	√	√	X	√	High
Danadevi *et al.* , 2003	X	√	X	√	X	X	NA	NA	√	√	√	High
McDermott *et al.* , 2014	√	X	√	√	√	X	√	√	√	X	√	High
Guo *et al.* , 2010	X	√	X	√	X	X	X	X	X	X	X	High
Chashschin *et al.* , 1994	X	√	X	√	√	X	X	X	√	√	√	High
Jelnes and Knudsen, 1988	X	√	X	√	X	X	NA	NA	√	√	X	High
Pietrzyk *et al.* , 1994	X	√	X	√	X	X	NR	NR	NR	NR	NR	High
Odland *et al.* , 1999	√	√	X	√	X	X	X	X	√	X	√	High
Odland *et al.* , 2004	√	√	X	√	X	X	X	X	√	X	X	High
Zheng *et al.,* 2014	√	√	X	√	X	X	√	X	X	√	X	High
Vaktskjold *et al.* , 2006	√	√	√	√	√	X	X	√	X	√	√	High
Vaktskjold *et al.* , 2007	√	√	√	√	√	√	√	√	√	√	√	Low
Vaktskjold *et al.* , 2008a	√	√	√	√	√	X	√	√	√	√	√	Low
Vaktskjold *et al.* , 2008b	√	√	X	X	√	X	√	√	√	√	√	High
Windham *et al.* , 2006	√	X	X	√	√	X	√	X	X	√	X	High

Notes:

NR = Not Reported; NA = Not Applicable; SES = Socioeconomic Status.

Green indicates that the study met the criterion. Red indicates that the study did not meet the criterion. Grey indicates high risk of bias. White indicates low risk of bias.

√ indicates that the study accounted for this aspect. X indicates that the study did not account for this aspect.

(a) Detailed information on criteria can be found in Section 4 of the text.

(b) For the category of "Health," a study had to measure and control for at least one health-related factor that could be associated with exposure and outcome, such as pre-existing disease status, maternal history of the outcome of interest, body mass index (BMI), or alcohol consumption during pregnancy.

(c) A study has a low risk of bias if it met all of the criteria in Tiers I and II, and also met three or more Tier III criteria (i.e., 5 of 5 confounders in addition to ≥ 2 of 3 of the other Tier III criteria); otherwise, we considered it to have a high risk of bias.

NR = Not Reported; NA = Not Applicable; SES = Socioeconomic Status.

Appendix A

Epidemiology Studies Evaluating Nickel Exposure and Reproductive and Developmental Effects

Table A.1 Epidemiology Studies Evaluating Nickel Exposure and Reproductive and Developmental Effects

Study	Location	Study Design	Cohort	# Cases	# Non-cases	Time Period of Study	Age	Sex	Exposure Measurement	Exposure Metric	Personal Measurement	Ni Conc	Assessed Co-exposures	Form of Ni Exposure	Outcome Assessed	Outcome Ascertainment	Statistical Analysis	Effect Measure	Confounders Adjusted For	Sensitivity Analysis
Bell *et al* ., 2010	US (CT and MA)	Cohort	Women with birth certificate information in NCHS	76,788	155,559	2000-2004	29.3	F	Regulatory monitor filters	Air monitors	No	No	No	NR	LBW	Birth certificate	Linear regression Logistic regression	% Change (β)	Apparent temperature by trimester Infant's sex Parity Nature of delivery Trimester prenatal care began Length of gestation Year of birth Mother's age Marital status Education Tobacco use during pregnancy Alcohol use during pregnancy Race	Linear regression with all 3 trimester variables Second stage analysis Interaction model (race)
Ebisu and Bell, 2012	US (CT, DE, MD, MA, NH, NJ, NY, PA, RI, VT, VA, DC, WV)	Cohort	Women with birth certificate information in NCHS	1,207,800	5,890,617	2000-2007	< 20 to ≥ 40	F	Regulatory monitor filters	Air monitors	No	No	Yes	NR	LBW	Birth certificate	Logistic regression	% Change (β)	Race Marital status Tobacco and alcohol consumption during pregnancy Maternal education Mother's age Infant sex Gestational length Trimester prenatal care began Birth order Nature of delivery Average AT for each trimester Season of birth Year of birth Regional indicators	Restrict to first births 2-pollutant models
Huang *et al.* , 2011	China (Ivliang region, Shanxi province)	Cohort	NR	NR	NR	2002-2004	NR	F	Soil	Soil samples	No	No	NR	NR	Neural tube defects	Medical records	Poisson	Prevalence	NR	NA
Bloom *et al.* , 2011	US (NY)	Cohort	Non-pregnant women discontinuing contraception for pregnancy	80	19	1996-1997	25-35	F	Blood	Whole blood	Yes	Yes	Yes	NR	Pregnancy	Positive pregnancy test	Cox PH model for discrete time (TTP)	% Change (β)	Baseline conc of metals PCBs Total serum lipids Age Parity Freq of intercourse during fertile window Alcohol use Cigarette use	
Danadevi *et al.* , 2003	India	Case-control	Workers at a welding plant	57	57	NR	32.3 (mean) 21-41 (range)	M	Blood	Whole blood	Yes	Yes	No	NR	Semen quality (sperm count, motility, morphology, defects)	Ejaculate	Chi Square test, Mann-Whitney U-test, Spearman's correlation analyses	r	Smoking Alcohol consumption	
McDermott *et al.* , 2014	US (SC)	Cohort	Mother-children pairs insured by SC Medicaid	1,146	8,774	1996-2002	< 18 to ≥ 34	F	Soil	Soil estimates from maternal address *via* Bayesian Kriging	No	No	No	NR	LBW	Birth certificate	Generalized additive model	OR	Infant sex Gestational age Maternal age Maternal race Parity Tobacco use Alcohol use	
Guo *et al.* , 2010	China (Guiyu)	Cross-sectional	Mother-children pairs in an e-waste recycling town	101	119	2008-2009	25.3 (mean Guiyu) 27.4 (mean control)		PcNi	Placenta	Yes	Yes	Yes	NR	Birth length BW Gestational age	Questionnaire survey	Independent sample t-test Chi Square test Spearman rank correlations	r		
Chashschin *et al.*, 1994	Russia	Cross-sectional	Mother-children pairs working in nickel hydrometallurgy refinery	356	342	NR	NR	F	Urine	Urine	Yes	Yes	No	NR	Abortion	Medical records		Prevalence odds ratio	Smoking Alcohol Intercurrent diseases	

Study	Location	Study Design	Cohort	# Cases	# Non-cases	Time Period of Study	Age	Sex	Exposure Measurement	Exposure Metric	Personal Measurement	Ni Conc	Assessed Co-exposures	Form of Ni Exposure	Outcome Assessed	Outcome Ascertainment	Statistical Analysis	Effect Measure	Confounders Adjusted For	Sensitivity Analysis
Jelnes and Knudsen, 1988	Denmark	Case-control	Men working at a welding plant	77	68	January 1987-July 1987	32 (median)	M	Blood Urine Semen	Blood Urine Semen	Yes	No	No	NR	Semen quality (sperm count, motility, morphology, defects)	Ejaculate	NR	NR	Smoking Age	
Pietrzyk *et al.* , 1994	Poland	Case-control	Mother-child pairs	178	NR	July 1992-June 1993	NR	F	Pubic and head hair	Prenatal	Yes	NR	No	Hair	Prematurity SGA	NR	ANOVA	F	NR	
Odland *et al.* , 1999	Russia and Norway	Cross-sectional	Mother-child pairs	265 137 (Russia) 128 (Norway)	NR	April 1993-June 1994	Norway (27.7 mean; 17-40 range) Russia (25.1 mean; 14-44 range)	F	Maternal and child urine	Urine	Yes	Yes	No	Urinary Ni	BW BMIC	Medical records	Linear regression	% Change (β)	Maternal urinary nickel Maternal height Maternal BMI Maternal urinary creatine Smoking Country	
Odland *et al.* , 2004	Russia and Norway	Cross-sectional	Mother-child pairs	262 148 (Russia) 114 (Norway)	NR	April 1993-June 1994	Russia: 25 (mean) Norway" 28.2 (mean)	F	Maternal blood Maternal and child urine Placenta	Maternal blood Maternal and child urine Placenta	Yes	Yes	No	Placenta	BW BMIC	Medical records	Linear regression	% Change (β)	Country Gestational age	
Zheng *et al.* , 2014	China	Case-control	Mother-child pairs who delivered at a Maternal and Child Health Hospital in Xiamen City	73	106	April - December 2010	< 25 to ≥ 30	F	Prenatal exposure	Umbilical cord blood	Yes	Yes	No	Cord blood	Adverse pregnancy outcomes: fetal distress, prematurity, macrosomia, composite outcome of any adverse pregnancy outcome	Medical records	Chi Square or Fisher's exact test Logistic regression	OR	Child's sex Maternal education Maternal monthly income	
Vaktskjold *et al.* , 2006	Russia	Nested Case-control	Mother-children pairs of female Ni plant workers within the KOLA Birth Registry	103	23,038	1995-2001	25 13-46 (range)	F	Employment Urine Quarterly stationary air monitors	Background (unexposed), low, and high exposures	Yes	Yes	No	Water soluble sub-fraction of the inhalable Ni aerosol fraction ($\mu g/m^3$) Urinary Ni (µg/L)	Genital malformations	Birth registry	Logistic regression	OR	Parity Maternal malformation Exposure to solvents at work Infectious disease prior to and during first trimester	Sub-analysis: undescended testes and hypospadias assessed as outcomes
Vaktskjold *et al.* , 2007	Russia	Nested Case-control	Mother-children pairs of female Ni plant workers within the KOLA Birth Registry	2,096	20,740	1995-2001	< 16 to > 34	F	Employment Urine Quarterly stationary air monitors	Background (unexposed), low, and high exposures	Yes	NR	No	Water soluble sub-fraction of the inhalable Ni aerosol fraction ($\mu g/m^3$) Urinary Ni (µg/L)	SGA	Birth registry	Logistic regression	OR	First delivery Regular maternal exposure to solvents at work Maternal age Maternal height Smoking Previous induced abortions Obvious signs of alcohol abuse during pregnancy	Exclude smoking Subanalysis: presence of 1+ genital defects in boys only
Vaktskjold *et al.* , 2008a	Russia	Nested Case-control	Mother-children pairs of female Ni plant workers within the KOLA Birth Registry	341	22,624	1995-2001	NR	F	Employment Urine Quarterly stationary air monitors	Background (unexposed), low, and high exposures	Yes	No	No	Water soluble sub-fraction of the inhalable Ni aerosol fraction ($\mu g/m^3$) Urinary Ni (µg/L)	Musculoskeletal defect	Birth registry	Multiple logistic regression	OR	1st delivery Tobacco smoking during pregnancy Regular exposure to solvents at work Alcohol abuse Maternal age	

Study	Location	Study Design	Cohort	# Cases	# Non-cases	Time Period of Study	Age	Sex	Exposure Measurement	Exposure Metric	Personal Measurement	Ni Conc	Assessed Co-exposures	Form of Ni Exposure	Outcome Assessed	Outcome Ascertainment	Statistical Analysis	Effect Measure	Confounders Adjusted For	Sensitivity Analysis
Vaktskjold *et al.* , 2008b	Russia	Case-control	Mother-children pairs of female Ni plant workers within the KOLA Birth Registry	184	1691	1996-2002	25.3	F	Employment Urine Quarterly stationary air monitors	Background (unexposed), low, and high exposures	Yes	No	No	Water soluble sub-fraction of the inhalable Ni aerosol fraction ($\mu g/m^3$) Urinary Ni (µg/L)	Spontaneous abortion	Questionnaire Birth registry	Logistic regression	OR	Maternal age History of induced abortion Previous delivery Heavy lifting at work Exposure to paints/solvents at work Maternal smoking	Analyses of SA in birth registry Additional adjustment for maternal smoking
Windham *et al.* , 2006	US (CA)	Case-control	Children living in CA	284	657	1994			Chemical emissions in a geographical area	Census tract of birth residence Air monitoring data (HAPs)	No	Yes	Yes	NR	ASD	Medical records	Logistic regression	OR	Maternal age Education Child's race	

Notes:

ANOVA = Analysis of Variance; ASD = Autism Spectrum Disorder; BMIC = Body Mass Index of Newborn Children; BW = Birth Weight; F = Female; HAP = Hazardous Air Pollutant; LBW = Low Birth Weight; M = Male; NA = Not Applicable; NCHS = National Center for Health Statistics; Ni = Nickel; NR = Not Reported; OR = Odds Ratio; PCB = Polychlorinated Biphenyl; PcNi = Placental Nickel; SA = Spontaneous Abortion; SGA = Small for Gestational Age; TTP = Time To Pregnancy.