EVIDENZE SULL'INTERAZIONE TRA ESPOSIZIONI AMBIENTALI NEI PRIMI 1000 GIORNI E RISCHIO INDIVIDUALE DI SALUTE IN AREE AD ELEVATO INQUINAMENTO INDUSTRIALE. UNA REVISIONE DELLA LETTERATURA

A cura del gruppo di lavoro **"I primi 1000 giorni"**

PRIMI
1000
GIORNI

Evidenze sull'interazione tra esposizioni ambientali nei primi 1000 giorni e rischio individuale di salute in aree ad elevato inquinamento industriale. Revisione della letteratura.
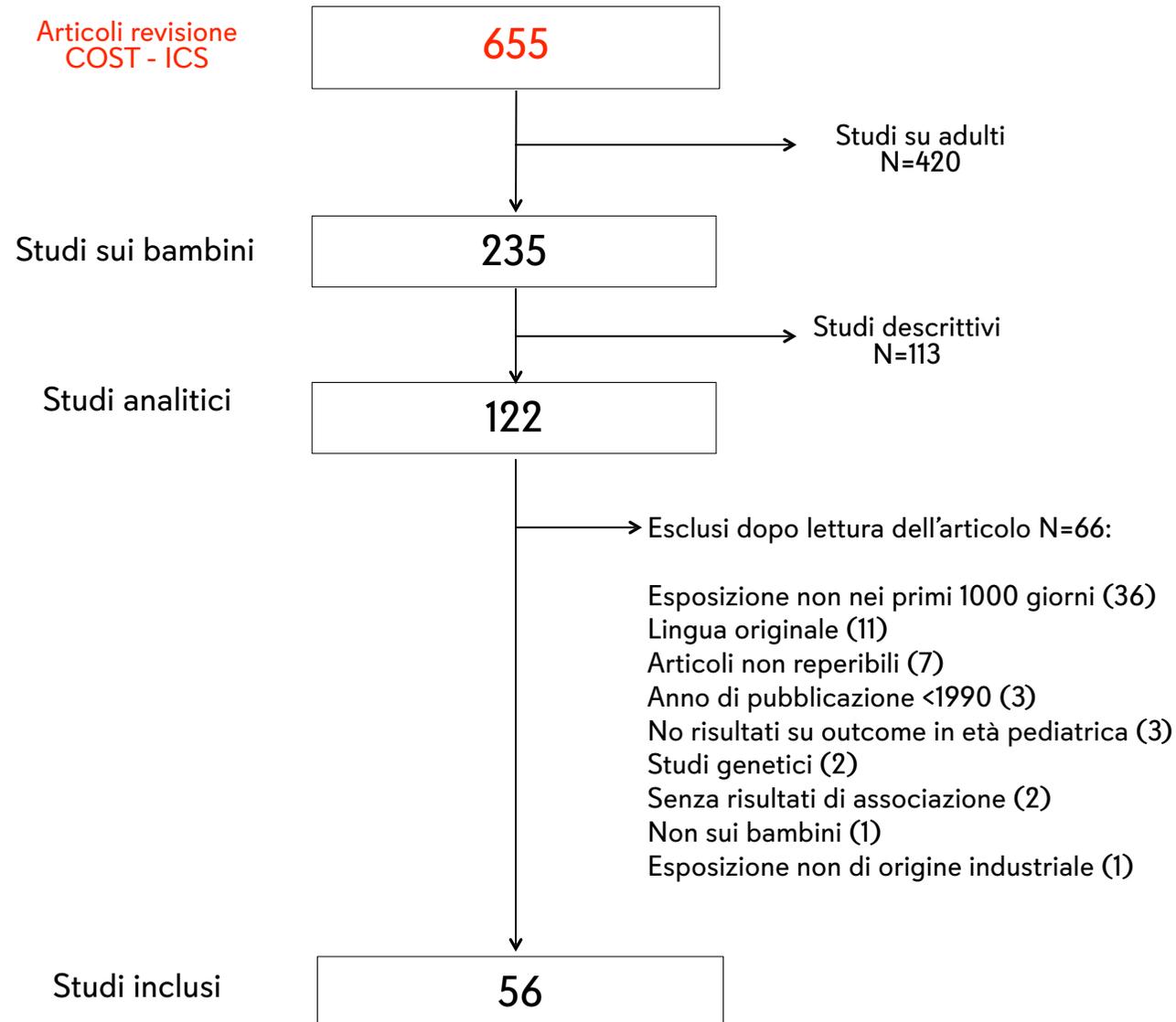
Strategia di ricerca utilizzata in MEDLINE

Database: **MEDLINE (OVID)** Date **June, 30th 2018**		
Exposure terms	1. ((industr* OR site OR plant OR plants OR mill OR farm*) adj4 (petroleum* or petro-chemical* or petroche-mical* OR pesticide* OR polymer* OR organochemical* OR colouring OR Pharmaceutical OR paper OR metallurg* OR potter* OR fertilizer* OR footwear OR shoe* OR lindane OR plastic OR rubber OR detergent* OR lubricant* OR lubricating* OR weapon* OR glass OR iron OR steel OR asbestos OR fluoroedenite OR amosite OR erionite OR balangeroite OR tremolite OR crocidolite OR chrysotile OR serpentine OR antigorite OR anthophyllite OR actinolite OR ferroactinolite OR amphibole*)).ab,ti 2. "mineral fiber*".ab,ti 3. industrial adj2 gas.ab,ti 4. agricultural adj2 chemicals.ab,ti 5. "waste oil".ab,ti 6. ((oil* OR petrol) adj3 (pollution OR refine* OR refining)).ab,ti 7. "fluoro edenite".ab,ti 8. "blue asbestos".ab,ti 9. 2 OR 3 OR 4 OR 5 OR 6 OR 7 OR 8 10. (industr* OR site OR plant OR plants OR mill OR farm*).ab,ti 11. 10 AND 9 12. ((power) adj2 (plant* OR station)).ab,ti 13. electricity adj2 production.ab,ti 14. industrial.ti,ab 15. 1 OR 11 OR 12 OR 13 or 14 16. ((mining OR quarries OR quarry OR waste OR incinerator* OR Landfill* OR port OR harbor OR harbour OR ship OR dock OR Superfund).ab,ti 17. 15 not "data mining".af	
	18. 16 OR 14	**165.710**

Outcome:	19. (Mortality OR Morbidity OR neoplasm* OR tumor* OR cancer* OR pregnan* OR respirator* OR cardiovasc* OR renal OR digestive OR congenital OR reproductive OR birth* OR death* OR neurologic*).ab,ti 20. MORTALITY.sh.	
	21. 18 or 19	**5.313.755**
Population:	22. Biomonitoring.ab,ti 23. (residence* or resident* OR residing OR residential* OR city OR cities OR community OR communities OR municipality OR neighbourhood* OR neighborhood* OR neighbouring OR neighboring OR urban OR exposed).ab,ti	
	24. 21 or 22	**1.242.508**
	25. 17 and 20 and 23	**6.711**
	25. 24 and "Humans" [Subjects]	**5.485**

Flow chart. Identificazione degli articoli inclusi nella revisione delle evidenze sull'interazione tra esposizioni ambientali nei primi 1000 giorni e rischio individuale in aree ad elevato rischio di inquinamento industriale.

Articoli revisione
COST - ICS

655

Studi su adulti
N=420

Studi sui bambini

235

Studi descrittivi
N=113

Studi analitici

122

Esclusi dopo lettura dell'articolo N=66:

Esposizione non nei primi 1000 giorni (36)
Lingua originale (11)
Articoli non reperibili (7)
Anno di pubblicazione <1990 (3)
No risultati su outcome in età pediatrica (3)
Studi genetici (2)
Senza risultati di associazione (2)
Non sui bambini (1)
Esposizione non di origine industriale (1)

Studi inclusi

56

Title	Authors	Setting	Study design	Sample size	Participants' characteristics	Exposures	Outcomes	Results
Maternal serum dioxin levels and birth outcomes in women of Seveso, Italy	Eskenazi et al. (2003)	Seveso area, Italy. Chemical factory explosion	cohort	981 women	Women enrolled in Seveso Women's Health Study (SWHS) were followed-up between 2008 and 2009. Inclusion criteria: >=40 years old in 1976, residence in zone A or B at the time of the explosion, adequate stored serum collected between 1976 and 1981	TCDD measured in sera collected between 1976 and 1981	spontaneous abortions, congenital anomalies and disorders, lowered birth weight, and shortened gestational age	there was no association of log10 TCDD with SAB [adjusted odds ratio (OR) = 0.8; 95% CI, 0.6-1.2], with birth weight (adjusted beta = -4 g; 95% CI, -68 to 60), or with births that were small for gestational age (SGA) (adjusted OR = 1.2; 95% CI, 0.8-1.8).

Maternal dioxin exposure and pregnancy outcomes over 30 years of follow-up in Seveso	Wesselink et al. (2014)	Seveso area, Italy. Chemical factory explosion	cohort	833 women	women enrolled in Seveso Women's Health Study (SWHS) were followed-up between 2008 and 2009. <u>Inclusion criteria</u>: >=40 years old in 1976, residence in zone A or B at the time of the explosion, adequate stored serum collected between 1976 and 1981	TCDD measured in sera collected between 1976 and 1981	spontaneous abortions, congenital anomalies and disorders, lowered birth weight, and shortened gestational age	no association between TCDD estimated at pregnancy and SAB, fetal growth, or gestational length. However, we found a nonsignificant inverse association between maternal 1976 serum TCDD and birthweight (adjusted β = –22.8, 95% CI: –80.1, 34.6).

In utero exposure to polychlorinated biphenyls and reduced neonatal physiological development from Guiyu, China	Wu et al. (2011)	Guiyu, CHINA	cross-sectional	167 mother-newborn pairs	<u>study period:</u> May-July 2007 108 participants from Guiyu (exposed) and 59 partecipants from Chaonan (not exposed) who voluntarily donated cord blood at delivery.	Polychlorinated biphenyls (PCBs) levels mesured from maternal blood collected at delivery	Premature delivery, low birth weight at term, and stillbirth.	Some individual PCB congeners were found to correlate with reduced neonatal height, weight, Apgar scores, gestational age, and body mass index (BMI). Difference of PPCBs level was found between normal birth and adverse birth outcomes (t=-2.262 p=0.030).

Association between maternal exposure to perfluorooctanoic acid (PFOA) from electronic waste recycling and neonatal health outcomes	Wu et al. (2012)	Guiyu, CHINA	cross-sectional	167 mother-newborn pairs	study period: May-July 2007 108 participants from Guiyu (exposed) and 59 partecipants from Chaonan (not exposed) who voluntarily donated cord blood at delivery.	perfluorooctanoic acid (PFOA) levels mesured from maternal blood collected at delivery	premature delivery, low birth weight at term, and stillbirth.	PFOA was negatively associated with gestational age [per lg-unit: β=–15.99 days, 95% CI, –27.72 to –4.25], birth weight (per lg-unit: β=–267.3 g, 95% CI, –573.27 to –37.18), birth length (per lg-unit: β=–1.91 cm, 95% CI, –3.31 to –0.52), and Apgar scores (per lg-unit: β=–1.37, 95% CI, –2.42 to –0.32), but not associated with ponderal index.

Mortality of a young population after accidental exposure to 2,3,7,8-tetrachlorodibenzodioxin	Bertazzi et al. (1992)	Seveso area, Italy	cohort	exposed: 20,000 not exposed: 95,339	study period: 1976-1986 19,637 people aged 1-19 years living in an area around Seveso at the moment of the accident. Exposed people lived in the A,B, R contamineted zones; 95 339 people of the same age living in the non contaminated portion of the health districts served as reference.	TCDD soil levels in the A zone: 15-580 $\mu g/m^2$; TCDD soil levels in the B zone: 1.7-4.3 $\mu g/m^2$; TCDD soil levels in the R zone: 0.9-1.4 $\mu g/m^2$	mortality owing to all causes, to all accidents and to all cancers	Five leukaemia deaths were observed, yelding relative risks of 2.1 (95% CI: 0.7-6.9), and 2.5 (95% CI: 0.2-27.0), respectively for males and females. Two lymphatic leukaemias among males yielded a RR = 9.6 (95% CI: 0.9-106.0). Mortality owing to congenital anomalies showed a nearly twofold increase in the contaminated area. Interpretation is limited by the small number of deaths.
Cancer in a young population in a dioxin-contaminated area	Pesatori et al. (1993)	Seveso area, Italy. Chemical factory explosion	cohort	exposed: 97,774 not exposed: 447,085	study period: 1976-1986 people aged 1-19 years living in an area around Seveso at the moment of the accident. Exposed people lived in the A,B, R contamineted zones; people of the same age living in the non contaminated portion of the health districts served as reference.	TCDD soil levels in the A zone: 15-580 $\mu g/m^2$; TCDD soil levels in the B zone: 1.7-4.3 $\mu g/m^2$; TCDD soil levels in the R zone: 0.9-1.4 $\mu g/m^3$	cancer incidence	overall cancer incidence was slightly but not significantly increased (RR= 1.2; 95% CI: 0.7-2.1). Ovary and uterine adnexa cancer, brain cancer, thyroid cancer, Hodgkin's lymphoma, lymphatic leukaemia, myeloid leukaemia have a not statistical significant Relative Risk (RR = 1.1; 95% CI : 0.3-4.1; RR =4.6 95%CI: 0.6-32.7; RR = 2.0 95%CI: 0.5-7.6; RR = 1.3 95%CI: 0.3-6.2; RR = 2.7 95%CI: 0.7-11.4).

Neonatal thyroid function in Seveso 25 years after maternal exposure to dioxin	Baccarelli et al. (2008)	Seveso area, Italy. Chemical factory explosion	cohort	1014 newborns exposed: 481 not exposed: 533	1,014 children born between 1994 and 2005 (56 from zone A, 425 from zone B, 533 from from the surrounding noncontaminated area -reference-).	b-TSH measurements obtained from the Lombardy Neonatal Screening Registry	livello di b-TSH nei neonati dopo prelievo di sangue	AS multivariate analysis revealed that, compared to the reference area, the relative odds of elevated b-TSH increased through contamination zones, with odds ratio (OR)=1.79 (95% CI 0.92–3.50) for zone B and OR = 6.60 (95% CI 2.45–17.8) for zone A (p= 0.002 for trend across zones).

| Neuropsychological measures of attention and impulse control among 8-year-old children exposed prenatally to organochlorines | Sagiv et al. (2012) | New Bedford, Massachusetts, USA. Superfund site | cohort | 578 children with CPT and 584 children with WISC-III | study period: 1993-1998. Inclusion criteria: English- or Portuguese-speaking mothers ≥ 18 years of age residing in one of four towns (New Bedford, Acushnet, Fairhaven, Dartmouth) near a PCB-contaminated harbor for at least the duration of pregnancy. | polychlorinated biphenyls (PCBs) and p,p´ dichlorodiphenyl dichloroethylene (p,p´DDE) levels mesured from cord blood collected at delivery. | attention and impulse control using a Continuous Performance Test (CPT) and components of the Wechsler Intelligence Scale for Children, 3rd edition (WISC-III). | Associations between PCBs and neuropsychological deficits were found but only among boys. Boys with higher exposure to ΣPCB4 had a higher rate of CPT errors of omission (RR for the IQR = 1.12; 95% CI: 0.98- 1.27) and slower WISCIII Processing Speed (change in score for the IQR = –2.0; 95% CI: –3.5, –0.4). Weaker associations were found for p,p´ - DDE. For girls, associations were in the opposite direction for the CPT and null for the WISC-III. |

| Risk of congenital anomalies around a municipal solid waste incinerator: a GIS-based case-control study | Vinceti et al. (2009) | Reggio Emilia, ITALY | case-control | 456 births and induced abortions | study period: 1998-2006 <br> case: 228 births and induced abortions with diagnosis of congenital anomalies from the registry of congenital malformations of the Emilia-Romagna Region (IMER) and from Hospital Discharge Directory of Emilia-Romagna residents (ICD9-CM diagnostic codes from 740.0 to 759.9).
 control: 228 births randomly selected among the livebirths without diagnosis of malformations, referred to the same hospital and born in the same year of the matched 'case' mother. | polychlorinated di-benzo-p-dioxins and dibenzofurans (PCDD/F) exposure. Three areas were identified based on the exposure: A (low exposure): 0-0.5 PCDD/F µg/m2; B (intermediate exposure): 0.51-1.0 PCDD/F µg/m2; C (high exposure): >1.0 PCDD/F µg/m2. A mother was considered exposed when her address was comprised within the intermediate and high (B and C) exposure areas, after inputting it in the GIS. | congenital anomalies | The OR for congenital anomalies was 1.49 (95% CI 0.70–3.19) in the medium exposure group and 0.66 (95% CI 0.25–1.79) in the high exposure group. Grouping together the two highest exposure levels, the OR in the overall exposed population resulted to be 1.11 (95% CI 0.60–2.04). The analysis for single anomaly categories showed an increased OR for chromosomal abnormalities in the middle exposure area (OR 2.53, 95% CI 0.88–7.24). |

| Maternal residence near municipal waste incinerators and the risk of urinary tract birth defects | Cordier et al. (2010) | Rhône-Alpes region, FRANCE | case-control | 530 infants | study period: 2001-2003 case: 304 live births, stillbirths or medical terminations of pregnancy between 2001 and 2003, diagnosed with a renal birth defect or obstructive uropathy and whose family resided in one of the eight administrative districts of the Rhone-Alpes region. control: a random sample of 226 population controls frequency matched for infant sex and year and district of birth. | Exposure to dioxins in early pregnancy at the place of residence, was predicted with second generation Gaussian modelling. Exposure to dioxins and metals 10 km away from the most heavily polluting solid waste incinerators was computed. Any family exposed to a level below this threshold was considered not exposed and above the threshold as exposed. | urinary tract birth defects, diagnosed with a renal birth defect (ICD-10 codes Q61.0, Q61.4, Q61.5, Q61.8, Q61.9) or obstructive uropathy (ICD-10 Q62). | Risk was increased for mothers exposed to dioxins above the median at the beginning of pregnancy (OR 2.95, 95% CI 1.47 to 5.92 for dioxin deposits). After adjusting for covariates the risk was reduced (OR 2.05, 95% CI 0.92 to 4.57). Compared with mothers who did not eat local food and lived in an area exposed below the median (reference category), consumers of local food in the same type of area had a reduced risk of urinary tract birth defects (OR 0.57, 95% CI 0.36 to 0.90). An increased risk, albeit not significant, was seen in consumers of local food living in areas with above-median exposure (OR 1.88, 95% CI 0.55 to 6.35), whereas nonconsumers living in exposed areas had an intermediate risk (OR 1.33, 95% CI 0.46 to 3.87). |

| Prenatal Arsenic Exposure and Birth Outcomes among a Population Residing near a Mining-Related Superfund Site | Henn et al. (2016) | Tar Creek Superfund site in Ottawa County, Northeast Oklahoma, USA | cohort | 622 mother–infant pairs | inclusion criteria: a) giving birth at Integris Hospital; b) intention to live within the study area for the next 2 years; c) not currently enrolled in the study with another child; and d) English-language proficiency sufficient to participate in the informed consent process. we excluded children with very low birth weights, multiple births, and those for whom data were missing on birth weight, gestational age, or all metal biomarker levels. | maternal blood and umbilical cord blood samples were collected at delivery (± 12 hr) and analyzed for total arsenic concentration | birth weight, gestational age, head circumference, and birth weight for gestational age. | we estimated negative associations between maternal blood arsenic concentrations and birth outcomes. In multivariable regression models adjusted for lead and manganese concentrations, an interquartile range increase in maternal blood arsenic was associated with –77.5 g (95% CI: –127.8, –27.3) birth weight, –0.13 weeks (95% CI: –0.27, 0.01) gestation, –0.22 cm (95% CI: –0.42, –0.03) head circumference, and –0.14 (95% CI: –0.24, –0.04) birth weight for gestational age z-score units. Associations between cord blood arsenic and birth outcomes were not statistically significant. |

The Port Pirie cohort study: maternal blood lead and pregnancy outcome	Mc Michael et al. (1986)	Port Pirie, AUSTRALIA	cohort	831 women	646 exposed mothers were resident in Port Pirie, whereas 185 not exposed mothers were from the surrounding rural area and neighbouring towns	lead blood concentration mesured during pregnancy (<14, 14-20 e 21-29, 30-36 settimane) and at delivery	spontaneous abortion, preterm delivery, premature rupture of membranes, congenital anomalies, late fetal death (LFD), birth weight, fetal lenght, head circumference, difficulties in conceiving	pre-term delivery was statistically significantly associated, in a dose-response manner, with maternal blood lead concentration at delivery. Outcomes of pregnancy for which no association with blood lead was detected were spontaneous abortion, low birthweight, intrauterine growth retardation, premature rupture of the membranes, and congenital anomalies.

Metal exposure and reproductive disorders in indigenous communities living along the Pilcomayo River, Bolivia	Stassen et al. (2012)	area along the Pilcomayo river, BOLIVIA	cross-sectional	1,395 women	study period: 1985-2006 exposed: 825 Weenhayek women living along the Pilcomayo river and resident in Capirendita, Tres Pozos and Tuunteytas villages not exposed: 570 Wichì women resident in the Lote, Misión Purísima, San Felipe e La Esperanza villages (Argentina)	lead and cadmium levels in hair of Weenhayek, Wichì adults and children.	reproductive variables: small families (fertility proxy) and fetal loss as at least one loss in the last two pregnancies. Developmental variables: congenital anomalies as presence of hemangiomas or ymphangiomas in any of the last two live-born children, delayed onset of walking in one or both of the last two children.	The Weenhayek communities studied had a higher prevalence of small families (OR 2.7, 95% CI 1.3–6.0) but no difference was found in the occurrence of reported fetal loss. However, there seemed to be a higher prevalence of the congenital anomalies studied (OR 2.6, 95% CI 0.7–9.2) among the Weenhayek. Their children also had an increased risk of delayed walking onset (OR 2.7, 95% CI 1.4–5.1).

Environmental exposure to lead and children's intelligence at the age of seven years. The Port Pirie Cohort Study	Baghurst et al. (1992)	Port Pirie, AUSTRALIA	cohort	494 children	seven years old children from the lead-smelting community of Port Pirie, Australia	exposure to lead was estimated from the lead concentrations in maternal blood samples drawn before and at delivery and from umbilical-cord blood, at the ages of 6 and 15 months and 2 years, and annually thereafter.	IQ of each child (verbal, performance, full-scale) was measured at the age of seven years by the revised version of the Wechsler Intelligence Scale for Children (WISC-R).	we found an inverse relations between IQ at the age of seven years and both antenatal and postnatal blood lead concentrations. For an increase in blood lead concentration from 10 to 30 micrograms per deciliter, expressed as the average of the concentrations at 15 months and 2, 3, and 4 years, the estimated reduction in the IQ was in the range of 4.4 points (95% CI 2.2-6-6) to 5.3 points (95% CI 2.8-7.8). This reduction represents an approximate deficit in IQ of 4 to 5%.

Child neurodevelopment in a Bolivian mining city	Ruiz-Castell et al. (2012)	city of Oruro, BOLIVIA	coorte	413 mothers and 246 children	<u>study period:</u> 2007-2009 Women were entrolled during preganncy in two hospital. <u>exclusion criteria:</u> woman's difficulty to understand he project and its objectives; women younger than 17 years; women with diagnosis of multiple pregnancies; women not resident of Oruro; preterm children; children with behavioral problems	blood maternal concentration of Pb,As,Cd,Sb,Cs,Zn,Fe, Cu,Se,Rb and Sr mesured during pregnancy	child neurodevelopment was assessed using Bayley Scales of Infant Development (BSID) at 10.5 and 12.5 months of age. The present paper focuses in particular on the mental and psychomotor scales (performance ability, memory and first verbal learning).	our results suggest that women from this mining area were not highly exposed. Surprisingly,at the observed low levels, lead was positively associated with the children's mental and psychomotor development assessed by BSID test (respectively p=0.034 and p=0.012).

Maternal and Cord Blood Manganese Concentrations and Early Childhood Neurodevelopment among Residents near a Mining-Impacted Superfund Site	Henn et al. (2017)	Tar Creek Superfund site in Ottawa County, Northeast Oklahoma, USA	cohort	224 mother–infant pairs	inclusion criteria: a) giving birth at Integris Hospital; b) intention to live within the study area for the next 2 years; c) not currently enrolled in the study with another child; and d) English-language proficiency sufficient to participate in the informed consent process.	manganese concentration in maternal and cord blood samples collected at delivery (± 12 hr)	children 2 years old neurodevelopment was evaluated using the Bayley Scales of Infant Development-II. This study is focused on mental (MDI) and psychomotor (PDI) development adjusted for age.	adjusting for lead,arsenic,and other potential confounders, an interquartile ranges (IQR) increase in maternal manganese was associated with –3.0 (95%CI:–5.3, –0.7) points on MDI and –2.3 (95%CI: –4.1, –0.4) points on PDI. Cord manganese concentrations were not associated with neurodevelopment scores. Cord/maternal and cord/total manganese ratios were positively associated with MDI [cord/maternal: b=2.6 95%CI: –0.04, 5.3; cord/total: b=22.0 95%CI: 3.2, 40.7] and PDI (cord/maternal: b=1.7 95%CI: –0.5, 3.9; cord/total: b=15.6 95%CI: 0.3, 20.9). Compared to mother–child pairs with low maternal and cord manganese, associations with neurodevelopment scores were negative for pairs with either high maternal, highcord,or high maternal and cord manganese.

Milestone achievement and neurodevelopment of rural Amazonian toddlers (12 to 24 months) with different methylmercury and ethylmercury exposure	Dorea at al. (2014)	state of Rondonia, in western Amazonia, BRAZIL	cross-sectional	309 children	children aged 12-24 months old in both rural villages (Bom Futuro n = 218; Itapuã n = 91) respectively populated by cassiterite miners and fishers.	MeHg (assessed from total hair Hg concentrations) and EtHg (assessed from vaccination cards).	The neurodevelopment of infants consisted of responses from GDS tests, applied to children during visits and developmental milestones (age the child first walked and first talked). The results were expressed as developmental quotients (DQ) or scores for each child: < 85 indicates a high probability of some impairment, 70-84 indicates moderate delay, <70 indicates severe delay.	A logistic regression model was applied to all infants after classification into two groups: above or below the median GDS schedules. Overall, there was no distinctive pattern of neurodevelopment associated with either HHg or EtHg exposure; however, nutritional status was significantly associated with GDS. In conclusion, milestone achievement was delayed in toddlers from tin-ore mining communities. Despite significantly higher exposure to both forms of organic Hg (MeHg from maternal fish consumption, and EtHg from TCV) in toddlers from the fishing village, significant differences were seen only among the proportions of most severely affected toddlers (GDS < 70).

Declining blood lead levels and changes in cognitive function during childhood: the Port Pirie Cohort Study	Tong et al. (1998)	Port Pirie, AUSTRALIA	cohort	375 children	children of the Port Pirie cogort followed up from birth to the age of 11 to 13 years	lead concentration mesured in: mothers blood during pregnancy and at delivery, mothers cord blood, children blood at 6, 15, 24 months and every year between 2-7 years and 11-13 years	cognitive function using the Bayley Mental Development Index at age 2 years, the McCarthy General Cognitive Index at age 4 years, and IQs from the Wechsler Intelligence Scale (revised version) at ages 7 and 11 to 13 years	Changes in IQ and declines in blood lead levels that occurred between the ages of 7 and 11 to 13 years (r= 0.12, P= .09) suggested slightly better cognition among children whose blood lead levels declined most. The cognitive deficits associated with exposure to environmental lead in early childhood appear to be only partially reversed by a subsequent decline in blood lead level.

Neurodevelopment outcomes in children exposed to organic mercury from multiple sources in a tin-ore mine environment in Brazil	Marques et al. (2014)	Bom Futuro (State of Rondonia), BRAZIL	cross-sectional	294 children	294 children <5 years aged, already included in the cohort study which enrolled mother-and-infant pairs in January 2006.	Hair-Hg (HHg) concentrations and total ethylmercury [from thimerosal-containing vaccines (TCVs)] were taken from infants and respective mothers during pregnancy.	Neurodevelopment using the Bayley Scales of Infant Development Second Edition (BSID-II) including the psychomotor developmental index (PDI) and the BSID-II mental developmental index (MDI score), adjusted for the age of the child, at 6 and at 24 months	Significant differences between boys and girls were observed for both MDI score (p = 0.0073) and MDI score (p = 0.0288) at 6 months but not at 24 months. Regression analysis showed that only in boys there was a significant interaction between MDI score and family income (b = 0.288, p = 0.018) or birth weight (b = -0.216, p = 0.036) at 6 months; at 24 months, however, only boys showed a significant association of both MDI score (b = -0.222, p = 0.045) and MDI score (b = -0.222, p = 0.045) with neonatal HHg. In boys, age of walking was associated with HHg (b = 0.188, p = 0.019) and breastfeeding (b = -0.282, p = 0.000), whereas for girls, age of walking was only associated with breastfeeding (b = -0.275, p = 0.001).

| Monitoring of lead load and its effect on neonatal behavioral neurological assessment scores in Guiyu, an electronic waste recycling town in China | Li et al. (2008) | Guiyu, CHINA | cross-sectional | 152 neonates | study period: July to October 2006 exposed: 100 full-term neonates were recruited from the the local hospital in Guiyu; not exposed: 52 full-term neonates were also recruited from another hospital (a neighboring town 20 km from Guiyu) | Lead levels from cord blood (CBPb) and meconium (MPb) of neonates. A questionnaire related to the exposure to lead of pregnant women was used as a survey of the neonates' mothers. | neonatal behavioral neurological assessment (NBNA). It contains five-clusters: behavior (six items), passive tone (four items), active tone (four items), primary reflexes (three items), and general assessment (three items). | Compared with the control group, neonates in Guiyu had significantly higher levels of lead (P < 0.01), that is correlated with their maternal occupation in relation to e-waste recycling. Neonates with high levels of lead have lower NBNA scores (P < 0.01). There was a statistically significant difference in NBNA scores between the Guiyu group and the control group by t test (P < 0.05). No correlation was found between CBPb and NBNA scores; however, a negative correlation was found between MPb and NBNA scores (P < 0.01). There is a correlation between relatively high lead levels in the umbilical cord blood and meconium in neonates and the local e-waste recycling activities related to lead contamination. |

Neurodevelopmental investigations among methyl-mercury-exposed children in French Guiana	Cordier et al. (2002)	Amerindian communities, FRENCH GUIANA	cross-sectional	378 children	<u>study period</u>: march-december 1997 156 children from the Upper Maroni (high exposure), 69 from Camopi on the Oyapock river (median exposure), and 153 from Awala on the Atlantic coast (low exposure).	Exposure to methyl-mercury was measured by determination of total mercury in the hair of the children and their mothers	Neurological evaluation was performed for all children aged 9 months to 6 years from the Upper Maroni and a random sample of the children from the other two communities, matched for age and sex. Neuropsychological investigation was performed on children aged 5 to 12 years.	After adjustment for potential confounders, we found a dose-dependent association between maternal hair mercury level and increased deep tendon reflexes (OR=5.20 95%CI 1.2-22) , poorer coordination of the legs, and decreased performance in the Stanford+Binet Copying score, which measures visuospatial organization. In this last test, the frequency of rotation errors was high in the 5+6 years age group and increased with mercury exposure. These associations depended on the sex of child and were stronger among boys.

Congenital anomalies among live births in a high environmental risk area--a case-control study in Brindisi (southern Italy)	Gianicolo et al. (2014)	Brindisi city, ITALY	case-control	1,759 newborns	study period: 2001-2010 cases: 357 newborns 0–28 days of age, born between 2001 and 2010 to mothers resident in Brindisi with congenital anomalies (CA). controls: 1402 newborns without a diagnosis of CA individually matched to cases for infant's gender and a socio-economic index calculated on mothers' residence during pregnancy. Controls and cases were also matched for the year of beginning of pregnancy.	four maternal exposure variables to air pollutants: SO2 and total suspended particulate(TSP) average concentration and 90th percentile over weeks 3–8 of pregnancy.	diagnosis of congenital anomalies (CA), congenital heart diseases (CHD) and ventricular septal defects(VSDs),	Exposure to the 90th percentile of SO2 was associated with CHDs (p for trend =0.01)and VSDs (p for trend<0.05). Findings for TSP were less consistent. In conclusion, in the studied area, maternal exposure to sulfur dioxide increased risk of CHD.

| Respiratory hospitalizations of children living near a hazardous industrial site adjusted for prevalent dust: a case-control study | Nirel et al. (2015) | Neot Hovav area, ISRAEL | case-control | 3,666 children | study period: 2004-2009 case: 3,608 residents of the Be'er Sheva sub-district within 40 km of the IP, aged 0–14 years who were admitted for respiratory illnesses between 2004-2009 control: 3,058 children admitted for non-respiratory conditions | (1) distance (less than 20 km/ more than 20 km) from the IP ('distance from the IP'); (2) presence (yes/no) of the dominant wind direction being from the IP toward a child's locality ('IP-residence wind direction') as a proxy measures for average exposure to ambient air pollution (the area >20 km from the IP was considered as non-polluted) | Respiratory hospitalizations of children between 2004-2009 | The association between hospitalization and residential distance from the IP was examined for three age groups (0–1, 2–5, 6–14) by logistic regressions. Infants in the first year of life who lived within 10 km of the IP had increased risk of respiratory hospitalization when compared with those living >20 km from the IP (adjusted OR = 2.07, 95%CI: 1.19–3.59). In models with both distance from the IP and PM10 the estimated risk was modestly attenuated (OR = 1.96, 95% CI: 1.09–3.51). Elevated risk was also observed for children 2–5 years of age but with no statistical significance (OR = 1.16, 95% CI: 0.76–1.76). |

Quantifying the impact of PM2.5 and associated heavy metals on respiratory health of children near metallurgical facilities	Dunea et al. (2016)	Targoviste, ROMANIA	cross-sectional	111 children	study period: 2013-2014. 111 children with ages between 0 and 10 years who live near metallurgical plants in Targoviste City.	concentrations of particulate matter with an aerodynamic diameter below 2.5 μm (PM2.5) and associated heavy metals (Pb, Cd, Cr, Ni, Fe) were estimated both by modelling emissions and by direct measuring. Using the spatial-temporal modeling technique we assigned an exposure value for each subject depending on the location.	occurrence of wheezing and hospital admission for wheezing	Significant correlations ($p < 0.01$) were observed between the locations of the children with respiratory issues (sensitive children: number of wheezing episodes; eosinophil count; immunoglobulin E (IgE) serum level; response to inhalation medication) and the PM2.5 multiannual average ($r = 0.985$) and PM2.5 maximum ($r=0.813$).

| Health effects for the population living near a cement plant: an epidemiological assessment | Bertoldi et al. (2012) | Mazzano and Rezzato municipalities, Lombardy, ITALY | case-control | 1385 children (0-14 anni) | case: 277 children (0-14 years) resident in Mazzano or Rezzato between 2002 and 2005 and admitted to hospital for respiratory didease of residents. controls: 1108 children randomly sampled from the total population, proportioning without individual matching for sex and age. | Nitrogen oxides (NOx) used as a proxy for cement plant emissions, were estimated by modelling emissions and by direct measuring, using mobile stations. Exposure was assigned to each subject using the spatial join technique and classified in 3 groups: Less exposed (E0) 81–110 μg/m3; Moderately exposed (E1) 111–150 μg/m3; Highly exposed (E2) >150 μg/m3 | hospital admission for respiratory diseases | The overall risks are higher: 1.67 for the moderately exposed group (E1) compared to the less exposed (E0), and almost double (OR 1.90) for the most exposed children (E2), with a significant p for trend (b0.001). The analysis stratified by sex showed that the risk appeared clear in males (but without an increasing exposure–response trend), while for the females the OR,was not statistically significant. Sub-analysis by age group showed lower risks (with a loss of statistical significance) for pre-school children (from 0 to 5 years), but even higher risks for schoolage children (6–14). |

| Risk of bone tumors in children and residential proximity to industrial and urban areas: New findings from a case-control study | Garcia-Perez et al. (2017) | SPAIN | case-control | 798 children | study period: 1996-2011 case: 114 incident cases of childhood (0–14 years) bone tumors from the Spanish Registry of Childhood Tumors control: 684 controls controls, individually matched by year of birth, sex and region of residence | (1) industrial distance, i.e. the distance between the subject's residence and any of the 1271 industrial facilities (recorded in the IPPC+E-PRTR 2009 database). These industries were classified into one of the 25 categories (2) urban distance, i.e. the distance between the subject's residence and the centroid of the town in which it resides. | childhood malignant bone tumors | Excess risk of bone tumors in children was detected for children close to industrial facilities as a whole (OR=2.33; 95%CI=1.17–4.63 at 3 km) – particularly surface treatment of metals (OR=2.50; 95%CI=1.13–5.56 at 2 km), production and processing of metals (OR=3.30; 95%CI=1.41–7.77 at 2.5 km), urban waste-water treatment plants (OR=4.41; 95%CI=1.62–11.98 at 2 km), hazardous waste (OR=4.63; 95%CI=1.37–15.61 at 2 km), disposal or recycling of animal waste (OR=4.73; 95%CI=1.40–15.97 at 2 km), cement and lime (OR=3.89; 95%CI=1.19–12.77 at 2.5 km), and combustion installations (OR=3.85; 95%CI=1.39–10.66 at 3 km), urban areas (OR=4.43; 95%CI=1.80–10.92). |

Residential proximity to environmental pollution sources and risk of rare tumors in children	Garcia-Perez et al. (2016)	SPAIN	case-control	3,899 children	study period: 1996-2011 case: 557 incident cases of childhood (0–14 years) rare tumors from the Spanish Registry of Childhood Tumors control: 3342 controls controls, individually matched by year of birth, sex and region of residence	(1) industrial distance, i.e. the distance between the subject's residence and any of the 1271 industrial facilities (recorded in the IPPC+E-PRTR 2009 database). These industries were classified into one of the 25 categories (2) urban distance, i.e. the distance between the subject's residence and the centroid of the town in which it resides.	five childhood cancers (retinoblastoma, hepatic tumors, soft tissue, germ cell tumors and other malignant epithelial neoplasms/ melanomas)	Children living near industrial and urban areas as a whole showed no excess risk for any of the tumors analyzed. However, isolated statistical associations were found between retino-blastoma and proximity to industries involved in glass and mineral fibers (OR=2.49; 95%CI=1.01–6.12 at 3km) and organic chemical industries (OR=2.54; 95%CI=1.10–5.90 at 2km). Moreover,soft tissue sarcomas registered the lower risks in the environs of industries as a whole(OR=0.59; 95%CI=0.38–0.93 at 4km).

| Childhood leukemia and residential proximity to industrial and urban sites | Garcia-Perez et al. (2015) | SPAIN | case-control | 13,826 children | study period: 1990-2011 case: 638 incident cases of childhood (0–14 years) cancer leukemia from the Spanish Registry of Childhood Tumors and for those Autonomous Regions control: 13,188 controls, individually matched by year of birth, sex and autonomous region of residence | (1) industrial distance, i.e. the distance between the subject's residence and any of the 1271 industrial facilities (recorded in the IPPC+E-PRTR 2009 database). These industries were classified into one of the 25 categories (2) urban distance, i.e. the distance between the subject's residence and the centroid of the town in which it resides. | childhood leukemia diseases coded as leukemias, myeloproliferative diseases and myelodysplastic diseases | Excess risk of childhood leukemia was observed for children living near (r2.5km) industries (OR=1.31; 95%CI=1.03–1.67) – particularly glass and mineral fibers (OR=2.42;95%CI=1.49–3.92), surface treatment using organic solvents (OR=1.87; 95%CI=1.24–2.83), galvanization (OR=1.86; 95%CI=1.07–3.21), production and processing of metals (OR=1.69; 95%CI=1.22–2.34), and surface treatment of metals (OR=1.62; 95%CI=1.22–2.15) – , and urban areas (OR=1.36; 95%CI=1.02–1.80). |

Association between residential proximity to environmental pollution sources and childhood renal tumors	Garcia-Perez et al. (2016)	SPAIN	case-control	1,491 children	study period: 1990-2011 case: 213 incident cases of childhood (0–14 years) renal cancer from the Spanish Registry of Childhood Tumors and for those Autonomous Regions control: 1,278 controls, individually matched by year of birth, sex and autonomous region of residence	(1) industrial distance, i.e. the distance between the subject's residence and any of the 1271 industrial facilities (recorded in the IPPC+E-PRTR 2009 database). These industries were classified into one of the 25 categories (2) urban distance, i.e. the distance between the subject's residence and the centroid of the town in which it resides.	childhood nephroblastoma and other non-epithelial renal tumors, renal carcinomas and unspecified malignant renal tumors	Excess risk of childhood renal tumors was observed for children living near (r2.5 km) industrial installations as a whole (OR=1.97; 95%CI=1.13-3.42) – particularly glass and mineral fibers (OR=2.69; 95%CI=1.19-6.08), galvanization (OR=2.66; 95%CI=1.14-6.22), hazardous waste (OR=2.59; 95%CI=1.25-5.37), ceramic (OR=2.35; 95%CI=1.06–5.21), surface treatment of metals (OR=2.25; 95%CI=1.24–4.08), organic chemical industry (OR=2.22; 95%CI=1.15-4.26), foodand beverage sector (OR=2.19; 95%CI=1.18-4.07), urban and waste-water treatment plants (OR=2.14; 95%CI=1.07–4.30) and production and processing of metals (OR=1.98;95%CI=1.03–3.82) –, and in the proximity of agricultural crops (OR=3.16; 95%CI=1.54–8.89 for children with percentage of crop surface >=24.35% in a 1-km buffer around their residences).

| Risk of neuroblastoma and residential proximity to industrial and urban sites: A case-control study | Garcia-Perez et al. (2016) | SPAIN | case-control | 2,786 children | study period: 1990-2011 case: 398 incident cases of childhood (0–14 years) neuroblastoma from the Spanish Registry of Childhood Tumors and for those Autonomous Regions control: 2,388 controls, individually matched by year of birth, sex and autonomous region of residence | (1) industrial distance, i.e. the distance between the subject's residence and any of the 1271 industrial facilities (recorded in the IPPC+E-PRTR 2009 database). These industries were classified into one of the 25 categories (2) urban distance, i.e. the distance between the subject's residence and the centroid of the town in which it resides. | childhood nephroblastoma neuroblastoma and other peripheral nervous cell tumors | Excess risk of neuroblastoma was detected for the intersection between industrial and urban areas: (OR=2.52; 95%CI =1.20–5.30) for industrial distance of 1 km, and (OR=1.99; 95%CI =1.17–3.37) for industrial distance of 2 km. By industrial groups, excess risks were observed near 'Production of metals' (OR=2.05; 95%CI=1.16–3.64 at 1.5 km), 'Surface treatment of metals' (OR=1.89; 95%CI=1.10–3.28 at 1 km), 'Mines' (OR=5.82; 95%CI=1.04–32.43 at 1.5 km), 'Explosives/pyrotechnics' (OR= 4.04; 95%CI=1.31–12.42 at 4 km), and 'Urban waste water treatment plants' (OR=2.14; 95%CI=1.08–4.27 at 1.5 km). |

Association of childhood leukemia with residential exposure to petrochemical air pollution in taiwan	Weng et al. (2008)	226 municipalities, TAIWAN	case-control	810 children	study period: 1995-2005 case: 405 eligible leukemia deaths occurring in people between 0 and 19 years of age controls: 405 all other deaths, excluding deaths due to neoplasms and diseases that were associated with respiratory problems. Control subjects were pair matched to the cases by gender, year of birth, and year of death.	The proportion of a municipality's total population employed in the petrochemical industry in a municipality was used as an indicator of a resident's exposure to air emissions from the petrochemical industry	leukemia mortality	subjects were divided into three levels (≤25th percentile; 25th–75th percentile; >75th percentile) according to the levels of the index of exposure. After controlling for possible confounders, results showed that children who lived in the group of municipalities characterized by the highest levels of petrochemical air pollution had a statistically significant higher risk of developing leukemia than the group that lived in municipalities with the lowest petrochemical air pollution levels.

Reproductive outcomes in an area adjacent to a petrochemical plant in southern Brazil	Oliveira et al. (2002)	municipality of Montenegro, southern BRAZIL	case-control	17,113 births	study period: 1983-1998 case: (1) newborns with major congenital malformations; (2) newborns with low birth weight (<2,500 g); and (3) stillborns (>500 g). control: the first newborns weighing ≥2,500 g without malformations and of case-matching sex.	distance of mother's residence from the petrochemical plant at the time of birth. Three regions were arbitrarily defined according to the plant proximity: Region 1: the nearest, in a perimeter of approximately 10 km from the plant; Region 2: intermediate, distant 10 to 20 km from the plant and including the municipality of Montenegro; Region 3: reference or unexposed area, extending beyond 30 km from the plant. The regions were further subdivided according to the prevailing wind direction in Region A (prevailing wind tunnel); Region B (lateral to A) and Region C, the same as Region 3, unexposed region.	newborns with major congenital malformations; newborns with low birth weight (<2,500 g) and stillborns (>500 g).	For unadjusted analysis, it was found a correlation between low birth weight and geographical proximity of mother's residence to the petrochemical plant (OR = 1.66; 95% CI = 1.01–2.72) or residence on the way of preferential wind direction (OR = 1.62; 95% CI = 1.03–2.56). When other covariates were added in the conditional logistic regression (maternal smoking habits, chronic disease and age), there was no association.

| Asthma prevalence and risk factors among children and adolescents living around an industrial area: a cross-sectional study | Ripabelli et al. (2013) | Termoli area, ITALY | cross-sectional | 89 children/ adolescent | study period: 2008-2009 1) A random sample of 89 children and adolescent aged 6 months and 14 years living in 8 municipalities (exposed:Termoli, not exposed: Campomarino, Guglionesi, Petacciato, Portocannone, San Giacomo degli Schiavoni, San Martino in Pensilis, and Ururi) was extracted from local register offices and were enrolled for the identification of cases through the administration of modified ISAAC questionnaires; 2) Pediatricians' databases on drug prescriptions in the study area (n=1,004), compared to a control area (n=920) with lower industrialization, were used to evaluate asthma prevalence in the pediatric population. | residence in the municipality of Termoli residence in other municipalities (reference) | asthma | All asthma cases were georeferenced based on the residence, however clusters were not found. Lifetime history of both atopic dermatitis and bronchitis were significantly related (respectively POR=8.78 95%CI=1.43-54.01; POR=17.23 95%CI=1.89-156.75) to asthma cases, as well as an elevated body mass index (POR=8.77 95%CI=2.40-31.97), whose association is consistent with prevalence data of overweight/obese children living in the study area. Moreover, being resident of the town of Termoli was associated to the occurrence of cases (POR=8.98 95%CI=1.17-68.91). |

Life prevalence of upper respiratory tract diseases and asthma among children residing in rural area near a regional industrial park: cross-sectional study	Karakis et al. (2009)	small agricultural communities in the regional industrial park (IP) in Negev, ISRAEL	cross-sectional	550 children	study period: 2002 children aged 0–14 years born in rural communities (kibbutzim). Informed consent was provided by: parents of the 333 children who lived in the proximal kibbutzim and parents of the 217 children who lived in the distal kibbutzim.	(1) distance (less than 20 km/ more than 20 km) from the IP ('distance from the IP'); (2) presence (yes/no) of the dominant wind direction being from the IP toward a child's locality ('IP-residence wind direction'); and (3) the child's mother having made odour complaints (yes/no) related to the IP ('odour complaints').	life prevalence (LP) of upper respiratory tract chronic diseases (URTCD) and asthma in children	Increased LP of URTCD in children of proximal localities was statistically significant when associated with odour complaints (OR=3.76; 95%CI=1.16-12.23). In proximal localities, LP of URTCD was higher (at borderline level statistical insignificance p=0.06) than in distant localities (OR=2.31; 95%CI=0.96-5.55). The following factors were found to be related to the excess of the LP of URTCD: (1) father's lower education (by distance: OR=2.62; 95%CI=1.23-5.57); by wind direction: OR=4.07; 95%CI=1.65-10.03); (2) in-vitro fertilization pregnancy (by distance: OR=3.03; 95%CI=1.17-7.87; by wind direction: OR=4.34; 95%CI=1.48-12.72). In proximal localities, the increase in asthma LP was associated with: (1) wind direction (OR=1.95; 95%CI=1.01-3.76); (2) a child's male gender (OR=2.95; 95%CI=1.48-5.87); and (3) a child's mother's having had an acute infectious disease during pregnancy (OR=4.84; 95%CI=1.33-17.63).

| Spatial Variability in ADHD-Related Behaviors Among Children Born to Mothers Residing Near the New Bedford Harbor Superfund Site | Vieira et al. (2016) | New Bedford, Massachusetts, USA | cohort | 573 children | children recruited at birth (1993–1998) whose mothers were living in 4 towns neighboring the New Bedford Harbor Superfund site (New Bedford, Dartmouth, Acushnet, and Fairhaven) during pregnancy. | Proximity to polychlorinated biphenyl–contaminated New Bedford Harbor (NBH) using geocoded coordinates for birth residences | ADHD-related behaviors at age 8 years using Conners' Teacher Rating Scale–Revised: Long Version (DSM-IV ADHD scale) | Models that adjusted for child's age and sex displayed significantly increased ADHD-related behavior among children whose mothers resided west of the NBH site during pregnancy. These spatial patterns persisted after adjusting for prenatal exposure to organochlorines and metals but were no longer significant after controlling for sociodemographic factors. |

Residential proximity to waste sites and industrial facilities and chromosomal anomalies in offspring	Brender et al. (2008)	Texas, USA	case-control	6467 newborn	<u>study period</u>: 1996-2000 <u>case</u>: 2099 births with chromosomal anomalies <u>control</u>: 4368 births without documented birth defects and without chromosomal anomalies, randomly selected from 1996–2000 live birth certificates and frequency-matched to case births by year of birth and public health region of maternal residence (11 regions in Texas).	Proximity to hazardous waste sites or industrial facilities (with reported air emissions, particularly solvents and heavy metals) using geocoded coordinates for birth residences. A distance of < 1 mile was used to define residential "proximity" to waste sites or industrial facilities. The referent group consisted of women who lived >=1 miles from these sites and facilities.	chromosomal anomalies (trisomy 21, trisomy 13, trisomy 18, autosomal deletion syndromes, balanced autosomal translocation in normal individuals, other conditions due to autosomal anomalies, monosomy X variants, Klinefelter variants and other sex chromosome anomalies)	With adjustment for confounders, maternal residence within 1 mile of a hazardous waste site (relative to farther away) was not associated with chromosomal anomalies in offspring except for Klinefelter variants among Hispanic births (OR=7.9, 95%CI=1.1–42.4). Women 35 years or older who lived within 1 mile of industries with emissions of heavy metals were two times more likely (95% CI=1.1–4.1) than women living farther away to have offspring with chromosomal anomalies including trisomies 13, 18, or 21 or sex chromosome abnormalities. Among women 40 years or older, maternal residence within 1 mile of industries with solvent emissions was associated with chromosomal anomalies in births (OR=4.8, 95%CI=1.2–42.8).

| Maternal residential proximity to waste sites and industrial facilities and oral clefts in offspring | Brender et al. (2006) | Texas, USA | case-control | 6149 new-born | study period: 1996-2000 case: 1781 births with oral clefts   control: 4368 births without documented birth defects and without congenital malformations (neural tube defects, conotruncal heart defects, oral clefts, and chromosomal anomalies) randomly selected from 1996–2000 live birth certificates and frequency-matched to case births by year of birth and public health region of maternal residence (11 regions in Texas). | Proximity to hazardous waste sites or industrial facilities (with reported air emissions, particularly solvents and heavy metals) using geocoded coordinates for birth residences A distance of< 1 mile was used to define residential "proximity" to waste sites or industrial facilities. The referent group consisted of women who lived >=1 miles from these sites and facilities | oral clefts (cleft palate without cleft lip and cleft lip without or with cleft palate) | Compared with women who lived farther, women who lived within 1 mile of these sites or facilities were not more likely to have offspring with oral clefts. Among women 35 years, oral clefts in offspring were associated with living within a mile of industrial facilities with reported air emissions (OR= 2.4, 95%CI=1.3–4.2), especially metals/smelters facilities (OR=15.0, 95%CI=2.8–151). |

Maternal residential proximity to waste sites and industrial facilities and conotruncal heart defects in offspring	Langlois et al. (2009)	Texas, USA	case-control	5612 new-borns	study period: 1996-2000 case: 1244 births with conotruncal heart defects control: 4368 births without documented birth defects from a larger project of residential proximity to environmental hazards and without congenital malformations (neural tube defects, conotruncal heart defects, oral clefts, and chromosomal anomalies) randomly selected from 1996–2000 live birth certificates and frequency-matched to case births by year of birth and public health region of maternal residence (11 regions in Texas).	Proximity to hazardous waste sites or industrial facilities (with reported air emissions, particularly solvents and heavy metals) using geocoded coordinates for birth residences. A distance of less than 1 mile was used to define residential "proximity" to waste sites or industrial facilities. The referent group consisted of women who lived 1 or more miles from these sites and facilities.	conotruncal heart defects, including subsets of specific defects	maternal residential proximity (living within 1 mile) to waste sites or industries with reported air emissions was not associated with risk of conotruncal heart defects (OR= 0.83, 95%CI= 0.54-1.27) or its subtypes in offspring, with the exception of truncus arteriosus which showed statistically elevated ORs with any waste site (crude OR=2.80, 95%CI=1.19-6.54) and with NPL sites (crude OR=4.63, 95%CI=1.18-13.15; aOR=4.99, 95%CI=1.26-14.51).

| Maternal residential exposure to hazardous wastes and risk of central nervous system and musculoskeletal birth defects | Marshall et al. (1997) | New York State, USA | case-control | 16,112 newborns | case: 3,676 central-nervous-system and musculoskeletal-defect births to residents of 18 counties in New York State; controls: 12,436 randomly chosen normal births | Proximity to hazardous waste sites or industrial facilities (with reported air emissions, particularly solvents, metals and pesticide) using geo-coded coordinates for birth residences. | central nervous system (CNS) defects, musculoskeletal (MUS) defects | Mothers who resided in areas assigned a medium or high probability of exposure to hazardous waste contaminants did not show an increased risk of either type of birth defects. After adjusting the resulting relative risks were as follows: CNS defects and exposure to solvents, 0.8 (95%CI=0.4-1.6); CNS and metals, 1.0 (95% CI = 0.7-1.7); musculoskeletal defects and solvents, 0.9 (95%CI = 0.5-1.3); musculoskeletal defects and pesticides, 0.8 (95% CI = 0.5-1.3) .With respect to CNS defects, there was an elevated risk associated with living near industrial facilities that emitted solvents (OR= 1.3 95%CI = 1 .0- 1.71) or metals (OR = 1.4, 95%C= 1. 0- 1.81) into the air. |

| Risk of malformations associated with residential proximity to hazardous waste sites in Washington State | Kuehn et al. (2007) | Washington State, USA | case-control | 327,099 children | study period: 1987–2001 <br> case: 55,775 <br> control: 271,324
 Controls were matched by birth year | Proximity to hazardous waste sites using geocoded coordinates for birth residences. | congenital malformations (from the hospital discharge records, or presence of a check-box on the birth certificate). | Relative to living >5 miles from a site, living<=5 miles was associated with increased risk of any malformations in offspring (for >2–<=5 miles: OR 1.15: 95%CI: 1.10-1.21; for >1–<=2 miles: OR 1.26, 95% CI:1.20-1.32; for >0.5–<=1 miles: OR 1.28, 95% CI: 1.22-1.35; for <=0.5 miles: OR 1.33, 95% CI: 1.27-1.40.). Risk estimates varied by urban vs. rural maternal residence and by specific malformation type. |

Maternal residential proximity to hazardous waste sites and risk for selected congenital malformations	Croen et al (1997)	California State, USA	case-control	study 1) 1,024 births study 2) 1,095 births	Authors selected case and controls from two previous studies: 1) 613 mothers delivered liveborn or stillborn infant with an neural tube defects-NTD, as well as those who had an NTD-affected pregnancy that was electively terminated after prenatal diagnosis. 611 eligible controls were non-malformed, singleton infants born alive in the same time period and geographical area as cases. 2) 772 women who delivered a liveborn or stillborn infant with a conotruncal heart defect or an oral cleft defect. 631 eligible controls were non-malformed liveborn infants delivered in the same time period and geographical area as cases.	maternal residential proximity to hazardous waste sites during the periconceptional period. "Exposed" subjects were those who resided in a census tract with a waste site (NPL site, non-NPL site, any site). "Unexposed" subjects were those residing in a "no waste site" tract. For analyses based on distance between residence and site, we computed the distance (miles) between each maternal residential address and waste site location. "Exposed" subjects were those with a maternal residence within 1 mile of a waste site. We assigned cases and controls with a maternal residence greater than 1 mile from any site to the "unexposed" category.	neural tube defects, conotruncal heart defects, and oral cleft defects	After controlling for several potential confounders, we found little or no increased risk for maternal residence in a census tract containing a site (OR = 0.9, 95% CI =0.7-1.3 for neural tube defects; OR = 1.3, 95% CI = 0.8-2.1 for heart cases; OR = 1.2, 95% CI = 0.8-1.8 for cleft) but elevated risks for neural tube defects (OR = 2.1, 95% CI = 0.6-7.6) and heart defects (OR = 4.2, 95% CI = 0.7-26.5) for maternal residence within 1/4 mile of a National Priority List site. Furthermore, we observed elevated ORs (>2.0) for neural tube defects and heart defects in association with maternal residence within 1 mile of National Priority List sites containing selected chemical contaminants.

Risk of congenital malformations associated with proximity to hazardous waste sites	Geschwind et al. (1992)	New York State, USA	case-control	27,115 births	study period: 1983-1984 case: 9,313 newborns with congenital malformations diagnosed at any time up to 2 years of age control: 17,802 healthy controls case exclusion criteria: Malformations were eliminated if: 1) they were considered redundant cases or if they did not have a valid birth certificate number; 2) the case infants were residents of New York City or were born in counties without census tracts; 3) multiple births as were all malformations listed on the Centers for Disease Control's "Exclusion List"	Proximity to Hazardous Waste Sites. "Exposed" subjects were those with a maternal residence within 1 mile of a waste site. We assigned cases and controls with a maternal residence greater than 1 mile from any site to the "unexposed" category.	malformations recorded in the Congenital Malformations Registry for the 1983 (1983-1985) and 1984 (1984-1986) birth cohorts.	maternal proximity to hazardous waste sites may carry a small additional risk of bearing children with congenital malformations OR = 1.12, 95% CI 1.06-1.18). Higher malformation rates were associated with both a higher exposure risk (no exposure risk: OR = 1.00; low exposure risk: OR = 1.09, 95% CI 1.04-1.15; high exposure risk: OR = 1.63, 95% CI 1.34-1.99) and documentation of off-site chemical leaks (not exposed: OR = 1.00; exposed, but no leaks at site: OR = 1.08, 95% CI 1.02-1.15; exposed, and leaks found at site: OR = 1.17, 95% CI 1.08-1.27).

| Elevated birth defects in racial or ethnic minority children of women living near hazardous waste sites | Orr et al. (2002) | California, USA | case-control | 28,401 children | study period:1983-1988 children were studied from a birth cohort including children (I)recorded on the birth or fetal death certificate as white-Hispanic, American Indian, Asian, Filipino, Hawaiian, Guamian, Samoan, Eskimo, Aleut, or Pacific Islander and (ii)resided in 24 selected counties in California at time of birth during 1983-1988 case: 13,938 minority infants with major structural birth defects (identified by the California Birth Defects Monitoring Program) whose mothers resided in selected counties at the time of delivery. control: 14,463 minority infants without birth defects who were randomly selected from the same birth cohort as the case subjects | The locations of all 84 National Priorities List (NPL) sites were geographically matched to 1980 census tracts. Each maternal residence was assigned the same potential-exposure category as its census tract. Residences were considered to be not exposed if they were in a census tract that did not contain an NPL site. | all birth defects combined diagnosed by the age of 1 year, MUS defects, integumental defects, heart or circulatory defects, CNS defects (and the CNS groupings NTDs, anencephaly, and spina bifida), oral cleft defects, and conotruncal heart defects. | Racial/ethnic minority infants whose mothers had been potentially exposed to hazardous waste were at slightly increased risk for birth defects (OR 1.12, 95% CI 0.98 ± 1.27) than were racial/ethnic minority infants whose mothers had not been potentially exposed. The greatest association was between potential exposure and neural tube defects (OR 1.54, 95% CI 0.93 ± 2.55), particularly anencephaly (OR 1.85, 95% CI 0.91 ± 3.75). The strongest association between birth defects and potential exposure was among American Indians/Alaska Natives (OR 1.19, 95% CI 0.62 ± 2.27). |

Incinerator pollution and child development in the taiwan birth cohort study	Lung et al. (2013)	TAIWAN	cohort	21,248 children	21,248 children born between October 2003 and January 2004. 953 (4.5%) lived near an incinerator	living within three kilometers of an incinerator	1) Taiwan Birth Cohort Study-Developmental Instrument (TBCS-DI) is a parental-report instrument evaluated at 6, 18, 36 months that measures child development on the basis of parental observation of the child's daily performance. It evaluates the child's development with respect to 4 dimensions: a) gross motor skills, b) fine motor skills, c) language/communication (language), and d) social/self-care ability (social). 2) Parental Concern Checklist	Living within three kilometers of an incinerator increased the risk of children showing delayed development in the gross motor domain at six and 36 months (β = –0.01, p = 0.061; β = –0.02, p = 0.007, respectively). In addition living in a city was associated with a higher likelihood of living near an incinerator (β = 0.02, p = 0.002). Living near an incinerator increased PCC regarding child development for mild U/DDD (β = 0.02, p = 0.032) and for moderate U/DDD (β = 0.02, p = 0.010). In addition to direct effects, living near an incinerator had an indirect effect on U/DDD through the mediating factor of breastfeeding, so children who were breastfed and living within three kilometers of an incinerator were at higher risk of showing mild U/DDD (β = 0.001).

Low birth weight and pre-term births among infants born to women living near a municipal solid waste landfill site in Montreal, Quebec	Goldberg et al. (1995)	Montreal, Quebec, CANADA	case-control	126,655 births	case: low birth weight, very low birth weight (<1500 g), preterm birth, and small for gestational age (<third percentile); control: for the low birth weight and very low birth weight analyses controls subjects were babies with a normal birth weight. For the pre-term babies analyses control subjects included infants with >= 37 weeks of gestational age. For the analyses of small gestational age controls were subjects above the third percentile. Inclusion criteria: all live births occurred among residents of Island of Montreal between 1979- 1989 and identified using the birth registration file of the province of Quebec. Exclusion criteria: multiple births, previous stillbirths, previous live births.	the exposure zones rapresented areas proximal and distal to the quarry. These zones were formed by grouping contiguous or nearly contiguous 3 character postal code areas. The highest exposure zone was divided into 2 subzone (high A and high B).	low birth weight (<2500 g), very low birth weight (<1500 g), preterm birth (<37 completed weeks), and small for gestational age (<third percentile) among infants born to women living near a municipal solid waste landfill site in the area of Montreal.	Low birth weight was significantly elevated in the exposure zone proximal to the site (adjusted OR = 1.20; 1107 exposed cases; 95%CI: 1.04-1.39). Excess risks were also observed for small for gestational age, but the association was not as strong as for low birth weight (adjusted OR = 1.09; 951 exposed cases; 95%CI: 0.96-1.24). No significant positive associations were observed for very low birth weight or for preterm birth.

Fetal deaths and proximity to hazardous waste sites in Washington State	Mueller et al. (2007)	Washington state, USA	case-control	77,992 infants	<u>study period:</u> 1987-2001 <u>case:</u> 7,054 fetal deaths at >=20 weeks during 1987-2001 <u>control:</u> 70,938 live-born infants during the same years <u>exclusion criteria</u>: gestational age < 20 weeks (the state's definition of reportable fetal death)	straight-line distances in miles between the mother's residence at the time of the live delivery or fetal death and the nearest hazardous waste site. We treated these distances as categorical variables (within 0.5 miles, > 0.5 to 1 mile, > 1 mile to 2 miles, > 2 miles to 5 miles, > 5 miles) and collapsed categories as necessary in some subanalyses for which data were limited.	fetal deaths	The risk of fetal death for women residing < 0.5 miles, relative to > 5 miles, from a hazardous waste site was not increased (adjusted OR = 1.06; 95% CI, 0.90-1.25). No associations were observed for any proximity categories: <= 5 miles from sites with contaminated air, soil, water, solvents, or metals; however fetal death risk increased among women residing < =1 mile from pesticide-containing sites (OR = 1.28;9 5%C I, 1.13-1.46).

Reproductive outcomes among former Love Canal residents, Niagara Falls, New York	Austin et al. (2011)	Love Canal Emergency Declaration Area (EDA), New York State, USA	cohort	1799 children and 980 woman	children born between 1960 and 1996 to women who conceived during or after their residence within the the Love Canal Emergency Declaration Area (EDA)—births before the mother lived at Love Canal were excluded. Two populations were selected as comparison groups: NYS (exclusive of the five boroughs of New York City) and Niagara County. In addition to comparisons with NYS and Niagara County, internal comparisons were conducted according to the potential for maternal exposure to Love Canal chemicals.	The primary exposure measure was constructed using residential locations and dates of occupancy. The EDA was divided into four geographic areas (tiers): Tiers1 and 2 were contiguous to or across the street from the landfill, and Tiers 3 and 4 were farther away. In addition, two distinct time periods were considered: 1942–1953 (Open Period, when the Canal was used for active dumping) and 1954 to the time of relocation of residents out of the EDA (Closed Period, when the Canal was covered with soil).	low birth weight, preterm birt, small for gestational age (defined as a singleton birth infant whose weight was in the lower 10% of the NYS reference population distributed by gestational week, infant sex, and calendar year group), congenital malformations (from the NYS Congenital Malformations Registry), proportion of male births higher than expected.	The results indicated a statistically significant elevated risk of preterm birth among children born on the Love Canal prior to the time of evacuation and relocation of residents from the Emergency Declaration Area, using Upstate New York as the standard population (standardized incidence ratio=1.40; 95% CI: 1.01,1.90). Additionally, the ratio of male to female births was lower for children conceived in the Emergency Declaration Area (sex ratio=0.94 versus sex ratio=1.05 in the standard population) and the frequency of congenital malformations was greater than expected among Love Canal boys born from 1983 to 1996 (standardized incidence ratio=1.50 when compared to Upstate New York), although in both cases the 95%CI included the null value. Finally, increased risk for low birth weight infants among mothers who lived closest to the Canal as children was found (odds ratio=4.68; 95%CI:1.24,17.66), but this estimate was limited due to small numbers(n=4).

| Morbidity among children living around clinical waste treatment and disposal site in the Northwest region of Cameroon | Mochungong et al. (2011) | Northwest Region of CAMEROON | cross-sectional | 20 children | study period: May to September 2008 Children aged <10 years were selected because of their fragility, developing immune systems and for the fact that they often play at such sites. exposed: children living in close proximity to a site where clinical waste is poorly treated and disposed. not exposed: children living in a separate neighbourhood, with an estimated 20 km from the exposed. This area had no hospitals or clinics and no waste dump site. | proximity to a site where clinical waste is poorly treated and disposed (<=20 km vs >20 km from the waste site) | episodes of intestinal, respiratory and skin infections using self-reported disease frequency questionnaires. | The risk ratios were 3.54 (95% CI, 2.19-5.73), 3.20 (95% CI, 1.34-7.60) and 1.35 (95% CI, 0.75-2.44) for respiratory, intestinal and skin infections respectively. Their respective risk differences were 0.47 (47%), 0.18 (18%) and 0.08 (8%). |

| Leukaemia in young children living in the vicinity of German nuclear power plants | Kaatsch et al. (2008) | 41 counties in the vicinity of 16 West German power plant sites, GERMANY | case-control | 2359 children | case: 593 children aged younger than 5 years (diseased between 1980 and 2003) registered at the german childhood cancer registry for leukaemia (GCCR). control: 1766 controls (1:3) matched for date of birth (as closely as possible), age, sex and nuclear power plant area (at the date of diagnosis) selected from the corresponding registrar's office. | residential proximity to the nearest nuclear power plant determined for each subject individually. The report is focused on cases in the inner 5-km zone around the plants. | leukaemia | All leukaemia combined show a statistically significant trend for 1/distance with a positive regression coefficient of 1.75 [lower 95%CI: 0.65]; for acute lymphoid leukaemia 1.63 (lower 95%CI: 0.39), for acute non-lymphocytic leukaemia 1.99 (lower 95%CI: 20.41). This indicates a negative trend for distance. Cases live closer to nuclear power plants than the randomly selected controls. A categorical analysis shows a statistically significant all leukaemias odds ratio of 2.19 (lower 95%CI: 1.51) for residential proximity within 5 km compared to residence outside this area. |

Leukaemia in young children in the vicinity of British nuclear power plants: a case-control study	Bithell et al. (2013)	GREAT BRITAIN	case-control	21,378 children	case: 10,618 children born and diagnosed under five in Great Britain for leukaemia and non-Hodgkin lymphoma (LNHL) between 1962 and 2007 control: 10,760 matched cancer-free controls similarly aged	residential proximity at birth and diagnosis to the nearest NPP. Proximity was defined as the reciprocal of the distance of the residential address at diagnosis to the nearest NPP operating before the birth of the child; this address was determined by the same criteria as for the birth addresses.	leukaemia and non-Hodgkin lymphoma (LNHL)	For 9821 children with LNHL under the age of 5 years, the estimated extra risk associated with residential proximity to an NPP at birth was negative-interpolated Odds Ratio (OR) at 5 km was 0.86 (95%CI=0.49–1.52). The comparison of 10,618 children with LNHL under five with 16,760 similarly aged children with other cancers also gave a negative estimate of the extra risk of residential proximity at diagnosis-interpolated OR at 5 km was 0.86 (95%CI=0.62–1.18).

Leukemia in Utah and radioactive fallout from the Nevada test site. A case-control study	Stevens et al. (1990)	Utah, USA	case-control	6507 individuals	case: 1177 deaths for leukemia control: 5330 other deaths Inclusion criteria: residents of Utah at the time of death and born before November 1 1958 and died between 1952-1981. the case subject, his/her spouse, or at least one parent had to be a member of the Church of Jesus Christ of Latterday Saints (LDS) during the period from 1950 to 1958, as determined by locating a record for the individual in the deceased membership file (DMF) of the LDS church.	3 levels of radiation dose: low dose (<=2.9 mGy), intermediate dose (3.0 to 5.9 mGy), and high dose (6.0 to 30.0 mGy).	leukemia	A weak association between bone marrow dose and all types of leukemia, all ages, and all time periods after exposure was found. This overall trend was not statistically significant, but significant trends in excess risk were found in subgroups defined by cell type, age, and time after exposure. The greatest excess risk was found in those individuals in the high-dose group with acute leukemia who were younger than 20 years at exposure and who died before 1964 (OR=7.82 ; 95% CI 1.90-32.2). There were 99 leukemia cases and 329 control subjects who were in utero during the fallout exposure period. Forty cases (40.4%) and 137 controls (41.6%) had received some irradiation while in utero: no associations were seen in this subgroup with the doses received in utero, during the first year of life, or thereafter, either separately or in a multivariate analysis of all three exposure variables.

Cancer incidence in the vicinity of Finnish nuclear power plants: an emphasis on childhood leukemia	Heinavaara et al. (2010)	FINLAND	cohort/ case control	<u>cohort analisys</u>: 32 children <u>case control analisys</u>: 80 children	children aged 0-14 years <u>cohort analisys</u>: 32 children <u>case control analisys</u>: 16 cases +64 controls	living within 15 km radius (<15 km) around the nuclear power plants (Loviisa and Olkiluoto)VS living in the 15–50-km zone (>=15 and <50 km)	leukemia and cancer incidence diagnosed during the follow-up of the cohort and obtained from the Finnish Cancer Registry	Cohort analisys : The two cohorts defined by censuses of 1980 and 1990 gave rate ratios of 1.0 (95% CI 0.3-2.6) and 0.9 (95% CI 0.2-2.7), respectively, for childhood leukemia in the population residing within 15 km from the NPPs compared to the 15–50 km zone. Case control analisys : The case–control analysis with 16 cases of childhood leukemia and 64 matched population based controls gave an odds ratio for average distance between residence and NPP in the closest 5–9.9 km zone (weighted by their relative durations) of 0.7 (95% CI 0.1-10.4) compared to >=30 km zone. Our results do not indicate an increase in childhood leukemia and other cancers in the vicinity of Finnish NPPs though the small sample size limits the strength of conclusions.

The psychological development of children from Belarus exposed in the prenatal period to radiation from the Chernobyl atomic power plant	Kolominsky (1999)	Chernobyl area , UKRAINE	cross-sectional	260 children	138 children at the age of 6–7 and 10–11 years, born during the period from May 1986 to February 1987 in the contaminated areas of Belarus (suffer prenatal radiation exposure at the time of the Chernobyl accident in 1986) were compared to a control group of 122 children of the same age (born in the period from May 1986 to February 1987), whose mothers had constantly lived in noncontaminated rural areas of Belarus.	living in the areas of Belarus contaminated by radionuclides following the Chernobyl accident VS living in the non contaminated rural area of Belarus	1) neurological and emotional-psychological development evaluated with the WISC-III test at 6–7 and 10–11 years; 2) psychiatric conditions assessed according to the diagnostic criteria of ICD-10 at 6–7 and 10–11 years	The exposed group manifested a relative increase in psychological impairment compared with the control group, with increased prevalence in cases of specific developmental speech-language disorders (18.1 % vs. 8.2% at 6-7 years ; 10.1 % vs. 3.3 % at 10-11 years) and emotional disorders (20.3 % vs. 7.4 % at 6-7years ; 18.1 vs. 7.4 % at 10-11 years). The mean IQ of the exposed group was lower than thatof the control group, and there were more cases of borderline IQ (IQ=70-79) (15.9 % vs.5.7 % at 6-7 years ; and 10.1 % vs. 3.3 % at 10-11 years).

The thyroid status of children and adolescents in Fukushima Prefecture examined during 20-30 months after the Fukushima nuclear power plant disaster: a cross-sectional, observational study	Watanobe et al. (2014)	Fukushima prefecture , JAPAN	cross-sectional	1,137 children	study period: between November 10th 2012 and September 30th 2013 (20–30 months after the accident). A total of 1,222 subjects in the Fukushima Prefecture (614 males, 608 females), who all were 18 years old or younger (including fetuses) at the time of the accident.	estimated ground deposition of 131I across Fukushima Prefecture based on the data reported elsewhere, employing empirical Bayesian kriging interpolation method. In the estimated map the radioactivity of 131I is decay-corrected as of March 15th 2011, at which time the majority of radioiodine was considered to have been deposited in Fukushima Prefecture.	1) thyroid ultrasonographyphyto detect thyroid nodules (if detected, were classified into solid nodules or cysts, and their size and location were recorded), 2) thyroid-related blood tests to mesure TSH, FT3, fT4, Tg, TgAb, and TPOAb (for the subjects aged 6 yr or older at the examinations), 3) and the Urinary iodine measurement (UIC)	We analyzed a possible relationship among thyroid ultrasonographic findings (1,137 subjects), serum hormonal data (731 subjects), urinary iodine concentrations (770 subjects), and iodine-131 ground deposition (1,137 subjects). We did not find any significant relationship among these indicators, and no participant was diagnosed to contract thyroid cancer.

| Residence in coal-mining areas and low-birth-weight outcomes | Ahern et al. (2010) | coal mining areas in West Virginia, USA | cross-sectional | 42,770 new-born-mother pairs | study period: 2005-2007 not exposed: 15,788 moderate exposed: 7,833 high exposed: 19,149 | residence in a country with a mining with zero, moderate, or high level of coal tonnage. High and moderate levels were based on a median split of total production over the years 2005 through 2007. | Low birth weight obtained from the West Virginia Birthscore Dataset | Mothers who were older, unmarried, less educated, smoked, did not receive prenatal care, were on Medicaid and had recorded medical risks, had a greater risk of low birth weight. After controlling for covariates, residence in coal mining areas of West Virginia posed an independent risk of low birth weight. OR for both unadjusted and adjusted findings suggest a dose response effect. Adjusted findings show that living in areas with high levels of coal mining elevates the odds of a low-birth-weight infant by 16%, and by 14% in areas with lower mining levels, relative to counties with no coal mining |

Prevalence of asthma and other respiratory symptoms in children living near and away from opencast coal mining sites	Pless-Mulloli et al. (2001)	five pairs of rural and semi-urban communities (or parts thereof) in Northern ENGLAND	cross-sectional	4860 children	4860 children aged 1-11 years from 5 socioeconomically matched pairs of communities close to (OC) and away from (CC) active opencast coal site. The criteria for the selection of sites were: (1) Distance between centre of the community and the site boundary less than 750 m; (2) No intervening dust source (i.e. major road, other industry); (3) Prevailing wind direction from the site to the community; (4) Site active at time of study and (5) Population size of community at least 2000, equivalent to 300 children.	currently living near an active opencast site. The duration of exposure varied with the childrens' age and with the lenght of activity at the opencast site (from 6 months to many years prior to the study).	wheezing, asthma, bronchitis and other respiratory symptoms occurred between 2 and 12 months before receipt a mailed questionnaire	The cumulative prevalence of wheeze varied from 30% to 40% across the ten communities, it was 36% in OC and 37% in CC. The cumulative prevalence of asthma was 22% in both OC and CC, varying between 12% and 24%. We found little evidence for associations between living near an opencast site and an increased prevalence of respiratory illnesses, or asthma severity. Some outcomes such as allergies, hayfever, or cough varied little across the study communities. Others, such as the use of asthma medication, the number of severe wheezing attacks in the past year or tonsillitis showed large variation.