AQME
Association québécoise des médecins pour l'environnement

Increasing nickel air standards in Quebec

Human health concerns

A policy brief and literature review
Submitted to the Government of Quebec
in the context of the public consultation on air quality standards for nickel
Draft regulation amending the *Règlement sur l'assainissement de l'atmosphère*

By the Association québécoise des médecins pour l'environnement (AQME)

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Presentation of the Association québécoise des médecins pour l'environnement

Officially created in 2018, the Association québécoise des médecins pour l'environnement (AQME) brings together hundreds of Quebec physicians concerned with environmental issues. AQME is particularly interested in the impacts of climate change on health, active and public transportation, pesticides, nature protection, and energy issues. AQME is the Quebec chapter of the Canadian Association of Physicians for the Environment, founded in 1993.

Executive Summary

Nickel: an air pollutant with carcinogenic potential

Air pollution is a major health issue causing 4,000 premature deaths per year in Quebec. Medical literature shows that air pollution can cause lung cancer, respiratory diseases such as asthma and cardiovascular disease. Recent studies have also linked air pollution to dementia in adults, cognitive impairment, and autism in children.

Over the past 15 years, pathological effects have been reported at ever lower concentrations of air pollutants, so that the World Health Organisation (WHO) has lowered its guideline values for the main pollutants in 2021, including fine particles (PM_{10} and $PM_{2.5}$). It is notably through these particles that nickel can enter the body through the respiratory tract.

The International Agency for Research on Cancer has classified various nickel compounds as human carcinogens. The most studied substances are nickel sulphate, nickel oxide, and nickel subsulfide. However, there are variations in the carcinogenic potency of the different compounds, with nickel subsulfide in its NiS2₃ form being recognized as the most potent.

Setting a safe standard for nickel

The World Health Organisation (WHO) and U.S. Environmental Protection Agency (EPA) carcinogenicity guidelines were estimated from human and animal studies and are based primarily on Ni_3S_2. The guideline values determined in the early 2000s were set at 2.5 ng/m^3 annual mean in PM_{10} for the WHO and 2 ng/m^3 annual mean in PM_{10} for the EPA. These values refer to the concentration at which a person exposed for 70 years has no more than a one in a million chance of developing cancer.

The guide values for respiratory effects were estimated from animal studies using nickel sulphate. In Europe, a scientific committee of the European Commission assessed that an annual standard of 20 ng/m^3 annual mean in PM_{10} would minimize the respiratory effects of nickel. The committee also estimated that this concentration would be protective against the carcinogenic effects of nickel, as the most carcinogenic compound, nickel subsulfide of the Ni_3S_2 type, accounted for no more than 10% of all nickel compounds in European air. Ontario chose to adopt the same annual standard, sharing a very similar air composition to Europe.

Type of nickel in the air in Quebec: a speciation study exists

Knowing the type and distribution of nickel compounds in the air in a given region is therefore essential to establish an appropriate standard to minimize health effects. Speciation studies allow, among other things, the breakdown of air pollutants to assess which specific compounds are present in the air. The *Fiche technique de la norme de qualité de l'atmosphère relative au nickel* of the Ministère de l'Environnement et de la Lutte contre les changements climatiques (MELCC) reports that no speciation studies for nickel have been conducted in Quebec. In reference to the absence of such a study, the *Revue toxicologique de l'encadrement réglementaire de l'industrie du nickel pour le volet air ambiant* (a document used as a reference by the MELCC) based its recommendations on the composition of European air (with a high nickel sulphate composition and a low concentration of less than 10% of Ni_3S_2 subsulfide).

However, a speciation study conducted by the MELCC in 2013 in Quebec City was brought to our attention. It shows that most of the atmospheric nickel present in Quebec City is neither in the form of a sulphate nor in the form of a Ni_3S_2 type subsulfide. Rather, it is in the form of **pentlandite**, a nickel-iron sulfide ($Ni_9Fe_9S_8$), which, according to the study, comes mainly from the activities of the Port of Quebec.

Pentlandite: what effects on human health?

Pentlandite, a nickel-iron sulfide, could potentially be carcinogenic as an increase in lung cancer has been reported in pentlandite miners.

Some people refer to a 1992 study on hamsters to claim that pentlandite is not carcinogenic. However, in our opinion, this study should be considered invalid due to a major methodological flaw. The study used two groups: a group exposed to pentlandite (the compound of interest), and a control group exposed to nickel subsulfide of the Ni_3S_2 type, which is already recognized as a carcinogen. However, the control group did not develop cancer significantly, demonstrating that the animal model used for the study was not adequate to reproduce the desired effect. This study cannot therefore be used as a reference point to justify the safety of pentlandite. **Given that the main form of nickel in the air in Quebec City, a nickel-iron sulfide, is a substance that has been studied very little, it seems unreasonable to us to base the Quebec nickel standard on nickel sulphate.**

Western Australia, which mines large quantities of nickel in the form of pentlandite, has instead chosen to adopt an annual nickel standard of 3 ng/m^3 in PM_{10} based on the WHO guideline value for the carcinogen nickel subsulfide.

Nuances and weaknesses of the identified studies on nickel

The European annual standard of 20 ng/m^3 is based essentially on clinical studies conducted by the *National Toxicology Program* (NTP) dating back to 1996. However, some more recent studies do not appear in the references listed in the *Revue toxicologique de l'encadrement réglementaire de l'industrie du nickel pour le volet air ambiant* published by the MELCC in 2018. These new studies report new potential harmful effects of atmospheric nickel that should be investigated, such as the accumulation of fat in the arteries (atherosclerosis), the passage of nickel to the brain via the olfactory nerve (creating deposits similar to those of Alzheimer's disease), an increase in asthma or an increase in autism spectrum disorders. The animal models used in the NTP studies were not adequate to detect these potential effects.

In addition, an epidemiological study in eight Canadian cities reported a statistically significant positive association between increased nickel concentration in fine particulate matter (PM) and non-accidental mortality, which is of particular concern.

Furthermore, the studies used to establish the European standard did not assess the potential synergistic effects of other inhaled pollutants with nickel. Fine particles, the category of pollutants in which nickel is found, are a mixture of several different substances, some of which are known to have synergistic effects with nickel.

A question of social and environmental justice

The population of Quebec City is located near the Port of Quebec, where nickel transshipment takes place, is already dealing with pollution levels that greatly exceed the new WHO standards for nitrogen oxides (NO_x) and fine particles (PM_{10} and $PM_{2.5}$). The low level of urban canopy in this section of the city contributes to these high levels of pollution as trees have the ability to reduce air pollutant levels. In addition, this population has one of the highest levels of socio-economic disadvantage and co-morbidities (presence of several chronic diseases) in the city. The issue of nickel pollution is an additional **social and environmental justice issue** for these sectors of the city.

An incomplete economic analysis

We consider the *Évaluation des impacts économiques de la norme et de l'industrie du nickel au Québec,* published in 2018 and commissioned by the Ministère de l'Économie et de l'Innovation, to be incomplete because it does not take into account the **health costs generated by the pollution of this industry**. A study conducted by Health Canada in 2021 reports that the economic value of the health impacts of air pollution is approximately 30 billion dollars per year in Quebec. In its submission to the Laurentia Project consultation, AQME estimated that an increase of only 4.2% in $PM_{2.5}$ would be equivalent to additional health impacts of about $33 million per year. These calculations show that even a small increase in air pollutant concentration can be associated with high health costs. It would be irresponsible not to take this into account in economic estimates.

Final remarks and recommendations

In conclusion, the lack of knowledge about the deleterious health effects of pentlandite, including probable carcinogenic risks, calls for great caution. The currently proposed annual standard of 20 ng/m^3 is certainly based on existing standards, but in environments where the air composition differs from that found in Quebec City. Moreover, it is important to consider the context of socio-economic disadvantage and environmental injustice of the population that will be most impacted by an increase in the authorized standards for nickel in the air in Quebec.

In light of these findings, we believe that the precautionary principle should be applied. We therefore make the following recommendations:

- Adopt an annual standard of 3 ng/m^3 in PM_{10}, as in Western Australia.
- Maintain the 24-hour standard of 14 ng/m^3 in PM_{10}.
- Conduct research into the potential harmful effects of pentlandite, using human epidemiological studies and appropriate animal models.
- Further investigate the potential synergistic effects of nickel with other air pollutants.
- Adopt the new WHO 24-hour and annual guideline values for other air contaminants [PM_{10}, $PM_{2.5}$, nitrogen dioxide (NO_2), ozone (O_3), sulfur dioxide (SO_2), carbon monoxide (CO)] to better protect human health.
- Assess the economic costs of health impacts associated with nickel pollution.
- Promote the implementation of practices that could reduce pollutant emissions associated with industrial activities.

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Introduction

Air pollution is a major public health concern in Quebec. Numerous clinical studies have demonstrated the negative impacts of air pollution on health and life expectancy in Quebec, in Canada and elsewhere in the world. Medical science has demonstrated negative health impacts even at levels that were considered very low only a few years ago, so much so that agencies such as the World Health Organization (WHO) have lowered the recommended standards for several air pollutants.

Situation profile: pollution, nickel, and health impacts

Before addressing the health impacts of nickel, we will briefly present the health impacts of fine particles (PM) because nickel in ambient air is a component of these fine particles. It is therefore appropriate, in our opinion, to assess the overall health issue of air pollution from the outset before addressing the specific case of nickel.

Health impacts of air pollution

In high-income countries such as Canada, air pollution has been associated with about 33% of cardiovascular disease, 16% of COPD (chronic obstructive pulmonary disease), 12% of lower respiratory tract infections and 8% of tracheal, bronchial and lung cancers.[1] In addition, a recent Quebec study, conducted on a cohort of 1,183,865 children followed from 1996 to 2011, all adjusted for socio-economic level, passive smoking, etc., showed that air pollution initiates asthma in children as a function of the dose and duration of exposure. The risk of asthma increases by 4 to 11% depending on the pollutant for each increase of one pollution quartile.[2]

[1] The Lancet Commission on Pollution and Health, Landrigan, Fuller et al, Published online 9 October 2017 http://dx.doi.org/10.1016/S0140-6736(17)32345-0. See Table 4 on page 28.
[2] Tétreault et al, Childhood Exposure to Ambient Air Pollutants and the Onset of Asthma: An Administrative Cohort Study in Québec, Environmental Health Perspectives, 2016, volume 124 | number 8: 1276-1282.

Air pollution is associated with 4,000 premature deaths per year in Quebec[3], twelve times more than those related to road accidents.[4] In addition, recent studies link air pollution to dementia,[5] [6] [7] autism and cognitive impairment in children. [8] [9] [10]

Some authors have recently reported an increase in mortality of COVID-19 in the presence of air pollution. [11][12] Finally, a recently published large study from the UK found that exposure to air pollution was associated with increased health service use for people with psychotic and mood disorders, such as depression. [13]

From a health perspective, the main air pollutants are fine particles (PM), NO_x and ozone. PM is a mixture of elements of which nickel can be a part. The finer a particle is, the more likely it is to penetrate deep into the lungs and spread to the rest of the body, causing, among other things, an inflammatory response and oxidative stress.

There are no threshold values for $PM_{2.5}$ below which there is no health impact.[14] Acute exposure to $PM_{2.5}$ can precipitate ischaemic heart disease, stroke, heart failure, venous thromboembolism, arrhythmias and increase hospital admissions, and cardiac mortality. Chronic exposure to $PM_{2.5}$ increases the risk of developing hypertension, diabetes, atherosclerosis, metabolic syndrome, and general cardiovascular mortality. The slope of the exposure-response curve for cardiovascular mortality is steep at low levels of annual $PM_{2.5}$ and flattens out at higher levels, meaning that the greatest health benefits result from interventions that reduce exposure to very low levels.[15]

Because of these health impacts at very low concentrations, the World Health Organization (WHO) has lowered its guidelines for annual $PM_{2.5}$ to 5 µg/m^3 and for 24-hours $PM_{2.5}$ to 15 µg/m^3 in 2021. These new guidelines are much lower than the MELCC's *Règlement sur l'assainissement de*

[3] Health Impacts of Air Pollution in Canada, Estimated Morbidity and Premature Deaths, Report 2021, Health Canada, Publ: 200424, 62 pages.
[4] https://saaq.gouv.qc.ca/fileadmin/documents/publications/bilan-routier-2019.pdf
[5] Living near major roads and the incidence of dementia, Parkinson's disease, and multiple sclerosis: a population-based cohort study, Cheng et al, The Lancet, 2017, http://thelancet.com/journals/lancet/article/PIIS01406736(16)323996/supplemental
[6] A critical review of the epidemiological evidence of effects of air pollution on dementia, cognitive function and cognitive decline in adult population, Juana Maria Delgado Saborita, Valentina Guercioe et al, Science of The Total Environment, Volume 757, 25 February 2021, 143734.
[7] Long-term exposure to ambient air pollution and risk of dementia: Results of the prospective Three-City Study, Marion Mortamaisa, Laure-Anne Gutierrez et al, Environment International, Volume 148, March 2021, 106376.
[8] Mild Cognitive Impairment and Dementia Involving Multiple Cognitive Domains in Mexican Urbanites. Calderón-Garcidueñas L1,2, Mukherjee PS3, Kulesza RJ4, Torres-Jardón R5, Hernández-Luna J6, Ávila-Cervantes R6, Macías-Escobedo E7, González-González O8, González-Maciel A8, García-Hernández K5, Hernández-Castillo A5, Villarreal-Ríos R9; Research Universidad del Valle de México UVM Group. J Alzheimers Dis. 2019;68(3):1113-1123. doi: 10.3233/JAD-181208.
[9] Air Pollution and Noncommunicable Diseases: A Review by the Forum of International Respiratory Societies' Environmental Committee, Part 2: Air Pollution and Organ Systems. Schraufnagel DE, Balmes JR, et al. Chest. 2019 Feb;155(2):417-426. doi: 10.1016/j.chest.2018.10.041.
[10] The impact of air pollution to central nervous system in children and adults. Sram RJ1, Veleminsky M Jr2, Veleminsky M Sr2, Stejskalová J2. Neuro Endocrinol Lett. 2017 Dec;38(6):389-396.
[11] Exposure to air pollution and COVID-19 mortality in the United States, Wu, Nethery et al, medRxiv, 2020.04.05.20054502
[12] Regional and global contributions of air pollution to risk of death from COVID-19, Andrea Pozzer et al. Cardiovascular Research, 2020. doi:10.1093/cvr/cvaa288
[13] Association between air pollution exposure and mental health service use among individuals with first presentations of psychotic and mood disorders: retrospective cohort study, Newbury, J B et al. British Journal of Psychiatry, 2021, pp 1-8.
[14] Interim Environmental Assessment Report - Laurentia Project: Deepwater Wharf in the Port of Quebec, 2020, 311 pages.
[15] Developing a clinical approach to air pollution and cardiovascular health, Hadley, Baumgartner and Vedanthan, Circulation, 2018, 137: 725-742.

l'atmosphère (RAA) standard (24-hours $PM_{2.5}$ at 30 µg/m^3) or the Canadian Council of Ministers of the Environment's Canadian Ambient Air Quality Standards (CAAQS) (annual $PM_{2.5}$ at 8.8 µg/m^3 and 24-hours $PM_{2.5}$ at 27 µg/m^3).

In addition to measures to reduce air pollutants at source, other measures can be put in place to capture air pollutants in urban areas, such as the conservation and planting of urban trees. Indeed, urban trees capture about 24% of air pollutants on average.[16] The mere presence of trees on a street can reduce particulate matter, the main air pollutant, by 50-75% for nearby residents and pedestrians.[17]

Health impacts of nickel

IARC (International Agency for Research on Cancer) has classified soluble and insoluble nickel compounds in Group 1 (carcinogenic to humans), and nickel alloys in Group 2B (possibly carcinogenic to humans). [18] The potential toxicity of nickel and nickel compounds depends on their physico-chemical characteristics, as well as the amount, duration of contact and route of exposure. Insoluble nickel compounds remain longer in the lungs and are associated with higher carcinogenicity. For example, insoluble nickel sulfide (Ni_3S_2) is a respiratory carcinogen. Nickel can enter the body through inhalation, ingestion with food and skin absorption; however, the most hazardous route of nickel exposure is inhalation.

Like other heavy metals, excessive exposure to nickel is thought to accelerate the process of oxidative stress and the generation of free radicals that cause DNA damage. [19] [20] In addition, because of its ability to penetrate the nucleus, nickel can affect gene expression, resulting in negative effects of nickel, including tumorigenic, abortifacient and teratogenic effects. In fact, all major body systems (including the nervous system, reproductive system, urinary system, gastrointestinal system, and respiratory system) are highly susceptible to nickel toxicity.

The medical scientific studies on the health impacts of nickel cited in the references of the *Revue toxicologique de l'encadrement réglementaire de l'industrie du nickel pour le volet air ambiant*[21] filed in 2018 do not seem to be more recent than 2011. However, since 2011, several studies have been published on nickel and should be taken into consideration knowing that since the last decade, medical science has demonstrated negative health impacts at very low concentrations of air pollutants, which has led to a downward revision of WHO guidelines for several pollutants: $PM_{2.5}$, PM_{10}, Ozone, NO_2, SO_2 and CO.

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[16] Planting Healthy Air, The Nature Conservancy, 2017, 128 pages.
https://thought-leadership-production.s3.amazonaws.com/2016/10/28/17/17/50/0615788b-8eaf-4b4f-a02a-8819c68278ef/20160825_PHA_Report_FINAL.pdf

[17] Air pollution abatement performances of green infrastructure in open road and built-up street canyon environments - A review, Abhijith, Kumar et al, Atmospheric Environment, Volume 162, August 2017, Pages 71-86

[18] Genchi, Carocci et al, 2020, Nickel: Human Health and Environmental Toxicology, International journal of Environmental Research and Public Health, 17, 679.

[19] Saghazadeha and Rezaei, Systematic review and meta-analysis links autism and toxic metals and highlights the impact of country development status: Higher blood and erythrocyte levels for mercury and lead, and higher hair antimony, cadmium, lead, and mercury, Progress in Neuro-Psychopharmacology and Biological Psychiatry. Volume 79, Part B, 3 October 2017, Pages 340-368.

[20] Cameron, Buchner and Tchounwou, Exploring the Molecular Mechanisms of Nickel-Induced Genotoxicity and Carcinogenicity: A Literature Review, Rev Environ Health. 2011; 26(2): 81-92.

[21] Bouchard, Toxicological review of the regulatory framework for the nickel industry for the ambient air component, 2018, 104 pages.

We listed 31 studies, literature reviews or meta-analyses of interest that are not cited in the *Revue toxicologique de l'encadrement réglementaire de l'industrie du nickel pour le volet air ambiant*, 19 of which were conducted in humans.

Human studies

Literature review

In a literature review published in 2020, the authors report that, depending on the dose and duration of exposure, as an immunotoxic and carcinogenic agent, nickel can cause a variety of health effects, such as contact dermatitis, cardiovascular disease, asthma, pulmonary fibrosis and respiratory tract cancers.[22] A high incidence of nasal and lung cancers has been observed in workers exposed to nickel and its compounds, and epidemiological studies have shown increased mortality from nasal and lung cancers in these workers. Water-insoluble nickel sulfide (NiS) and water-soluble nickel sulphate ($NiSO_4$) and nickel chloride ($NiCl_2$) are all carcinogenic to humans, although the insoluble nickel compounds are more carcinogenic than the soluble compounds. Recently, researchers attempting to characterize nickel's ability to induce cancer found that epigenetic alterations induced by nickel exposure can disrupt the genome. [22]

Other health effects have also been reported for nickel.[22] Water-soluble nickel compounds are absorbed by the lungs and eliminated by the kidneys. They can cause irritation of the nose and sinuses and can also lead to loss of smell and perforation of the nasal septum. Nickel nanoparticles have been associated with toxicity in embryos and teratogenic effects in fetuses. Studies have also reported neurotoxic effects. Although the molecular mechanisms of nickel-induced neurotoxicity are not yet clear, an important role is due to oxidative stress and mitochondrial dysfunction. Finally, among metals, nickel is the most frequent cause of metal allergy. Approximately 10-15% of the world's population suffers from a nickel allergy.

Respiratory system

Published in 2015, a review of the literature on the respiratory effects of metals in ambient particulate matter found that most studies showed an increased risk of respiratory morbidity with increasing metal concentrations, particularly with nickel.[23]

In another study published in 2018, the lung function of students was assessed at sites with similar $PM_{2.5}$ concentrations but varying concentrations of different metals.[24] Nickel concentrations in $PM_{2.5}$ ranged from 2.4 to 6.8 ng/m^3. Higher concentrations of nickel in ambient air were associated with decreased lung function in male students.

In a study published in 2016, Italian researchers sought to characterize the association between metal levels in personal air and respiratory health in Italian adolescents living in communities with

[22] Genchi, Carocci et al, 2020, Nickel: Human Health and Environmental Toxicology, International journal of Environmental Research and Public Health, 17, 679.
[23] Gray DL, Wallace LA, Brinkman MC, Buehler SS, La Londe C. Respiratory and cardiovascular effects of metals in ambient particulate matter: a critical review. Rev Environ Contam T. 2015;234:135-203.
[24] Huang, Chang et al, Metal composition of ambient PM2.5 influences the pulmonary function of schoolchildren: A case study of school located nearby of an electric arc furnace factory, Toxicology and Industrial Health, 2018, Vol. 3494), 253-261.

and without historical and current ferroalloy activity.[25] In the three communities studied, nickel concentrations ranged from 1.97 ng/m^3 for the community with no ferroalloy activity to 3.36 and 3.70 ng/m^3 for the two communities with historical ferroalloy activity. In adjusted models including PM_{10} as a co-pollutant, the researchers found a significant association between nickel concentrations (RR: 1.11, 95% CI [1.03, 1.21] per 4 ng/m^3 increase) and parental reporting of asthma. They also found significant associations between increased nickel and an increased risk of using asthma medication in the past 12 months (RR: 1.13, 95% CI [1.01, 1.27]).

Another US study published in 2009 compared temporal associations between $PM_{2,5}$, nickel in ambient PM2.5 and longitudinal reports of respiratory symptoms in young children up to 24 months of age.[26] Of all the pollutants assessed, the largest effect estimates were observed in association with nickel exposure. In models adjusted for sex, ethnicity, postnatal exposure to ambient tobacco smoke and calendar time, an increase in ambient nickel concentration in the interquartile range (IQR) (0.014 µg/m^3) was significantly associated with a 28% increased likelihood of wheezing in very young children (P = 0.0006). These results were robust to the inclusion of co-pollutants.

Nervous system

In a literature review published in 2001, the authors report anosmia and hyposmia in workers who chronically inhaled cadmium or nickel compounds and nasal cancers in workers who chronically inhaled certain nickel or chromium compounds. [27] In animals, several metals (e.g. aluminium, cadmium, cobalt, mercury, manganese, nickel, zinc) have been shown to pass through the olfactory receptor neurons from the nasal cavity to the olfactory bulb via the olfactory sieve plate.[28] Some metals (e.g. Mn, Ni, Zn) can cross the synapses of the olfactory bulb and migrate via secondary olfactory neurons to distant nuclei in the brain. After nasal instillation of a metal-containing solution, transport of the metal via olfactory axons can occur rapidly, within hours or days (e.g. Mn), or slowly, over several days or weeks (e.g. Ni). The authors conclude that the sense of smell is often considered unimportant for humans, whereas it is obviously vital for animals, fish, birds and insects. It is increasingly recognised that olfaction alerts people to danger (fire, toxic fumes, leaking gas, spoiled food, faecal contamination), affects appetite and nutrition (especially in the elderly), and contributes to psychological well-being and quality of life (appreciation of wines, foods, flowers, scents). Interest in olfaction has been stimulated by suggestions that hyposmia may be an early manifestation of Parkinson's and Alzheimer's disease.

In a literature review published in 2012 on the neurotoxicity of air pollutants, the authors consider that the "nose-brain" interaction as a pathway for air pollutants is a topic of emerging interest that deserves further research, especially considering the possibility that toxic components may be transported to target areas of the brain.[29] In vivo and in vitro data confirm the epidemiological evidence of neurotoxicity of air pollution exposure, with an important role played by the olfactory tract. Although the mechanisms underlying air pollution-induced central nervous system pathology

[25] Rosa, Benedetti et al., 2016, Association between personal exposure to ambient metals and respiratory disease in Italian adolescents: a cross-sectional study, BMC Pulmonary medicine, 16: 6.
[26] Patel MM, Hoepner L, Garfinkel R, Chillrud S, Reyes A, Quinn JW, et al. Ambient metals, elemental carbon, and wheeze and cough in New York City children through 24 months of age. Am J Respir Crit Care Med. 2009; 180(11):1107-13.
[27] Sunderman. Review: Nasal Toxicity, Carcinogenicity, and Olfactory Uptake of Metals, Annals of Clinical & Laboratory Science,vol. 31, no. 1, 2001
[28] Sunderman. Review: Nasal Toxicity, Carcinogenicity, and Olfactory Uptake of Metals, Annals of Clinical & Laboratory Science,vol. 31, no. 1, 2001
[29] Lucchini, Dorman et al, NEUROLOGICAL IMPACTS FROM INHALATION OF POLLUTANTS AND THE NOSE-BRAIN CONNECTION, Neurotoxicology. 2012 August; 33(4): 838-841. doi:10.1016/j.neuro.2011.12.001.

are poorly understood, new data suggest that microglial activation may be a key element, with an important contribution from conditions that predispose the individual to oxidative stress. The early data also suggest that children may be particularly exposed to air pollution, as childhood and adolescence are crucial periods of brain development, associated with dynamic behavioural, cognitive and emotional changes.

In a study published in 2006, US researchers explored possible associations between autism spectrum disorders (ASD) and environmental exposures.[30] Mean ambient air nickel concentrations were 4.3 ng/m^3 for autism cases and 3.7 ng/m^3 for control cases. Adjusted relative risks expressed as *adjusted odds ratios* (AORs) were 50% elevated in the upper quartile for chlorinated solvents and heavy metals [95% confiance intervals (CIs), 1.1-2.1], but not for aromatic solvents. Adjustment for these three groups simultaneously led to a decrease in risk for solvents and an increase in risk for metals (AOR for metals: fourth quartile = 1.7; 95% CI, 1.0-3.0; third quartile = 1.95; 95% CI, 1.2-3.1). The individual compounds that contributed most to these associations were mercury, cadmium, nickel, trichloroethylene and vinyl chloride. Their results suggest a potential association between autism and estimated ambient air concentrations of nickel around the birth residence.

Furthermore, in a meta-analysis published in 2017 on links between autism and metals, the authors report that an initial analysis of eight comparisons revealed higher levels of nickel in hair in patients with autism than in control subjects. [31] However, the difference did not remain significant after one study was excluded as an outlier. The authors conclude that further studies are needed.

In a study published in 2018, US researchers assessed the potential links between autism and 155 ambient air toxins in over 3000 participants from nearly 1500 families.[32] Estimated ambient levels of nickel were not reported in the study. Although the researchers did not confirm associations with several metals, including nickel, and volatile organic compounds detected in previous studies, they felt that their null results cannot be considered definitive given potential exposure measurement error and differences in population and analytical design.

Cardiovascular system

In a US study published in 2009, researchers examined whether the variation in relative risks (RRs) of cardiovascular and respiratory hospitalisation associated with ambient exposure to total PM mass $_{2,5}$ reflects differences in the chemical composition of $PM_{2.5}$.[33] The mean concentration of nickel in $PM_{2,5}$ in the 106 US counties included in the study was 2 ng/m^3. They found a positive and statistically significant association between county-specific estimates of the short-term effects of $PM_{2,5}$ on cardiovascular and respiratory hospitalizations and the levels of nickel in county-specific $PM_{2,5}$.

[30] Windham, Zhang et al, Autism Spectrum Disorders in Relation to Distribution of Hazardous Air Pollutants in the San Francisco Bay Area, Environ Health Perspect 114:1438-1444 (2006). doi:10.1289/ehp.9120 available via http://dx.doi.org/

[31] Saghazadeha and Rezaei, Systematic review and meta-analysis links autism and toxic metals and highlights the impact of country development status: Higher blood and erythrocyte levels for mercury and lead, and higher hair antimony, cadmium, lead, and mercury, Progress in Neuro-Psychopharmacology and Biological Psychiatry. Volume 79, Part B, 3 October 2017, Pages 340-368.

[32] Kalkbrenner, Windham et al, Air Toxics in Relation to Autism Diagnosis, Phenotype, and Severity in a U.S. Family-Based Study. Environmental Health Perspectives, 12 Mar 2018, 126(3):037004, DOI: 10.1289/ehp1867

[33] Bell ML, Ebisu K, Peng RD, Samet JM, Dominici F. Hospital admissions and chemical composition of fine particle air pollution, 2009, Am J Respir Crit Care Med, 179(12): 1115-20.

In a Canadian study published in 2018, 53 healthy non-smoking subjects were exposed to fine particles containing various metals including nickel at a concentration of 32.5 ng/m^3 in the combined particles.[34] A statistically significant increase of 5.3% in vascular endothelial growth factor (VEGF), a biomarker of blood inflammation, was observed one hour after nickel exposure.

In a study published in 2021, US researchers assessed which elementary components of the $PM_{2,5}$ mass are responsible for the previously reported associations between PM and$_{2,5}$ neonatal blood pressure.[35] They studied 1131 mother-infant pairs by measuring systolic (SBP) and diastolic (DBP) blood pressure at a mean age of 30 hours and mean exposures during the 2-7 days prior to birth for different components of $PM_{2,5}$. The mean level of nickel was 4.2 ng/m^3 in $PM_{2,5}$. They found that higher concentrations of nickel were associated with significantly higher SEP and DBP in neonates. They conclude that, since higher blood pressure in childhood is a predictor of hypertension in adulthood and cardiovascular disease later in life, nickel-associated increases in blood pressure in newborns could potentially contribute to increased cardiovascular health risks in later life.

Endothelial growth factor

A translational pilot study, published in 2013, was conducted among women residing in Jinchang and Zhangye, China, to test the hypothesis that a specific chemical component of $PM_{2,5}$ is responsible for PM-related$_{2,5}$ cardiovascular disease.[36] Daily ambient and personal exposures to PM and$_{2,5}$ 35 components were measured in the two cities. A total of 60 healthy, non-smoking adult residents were recruited to measure biomarkers of inflammation. Ambient $PM_{2,5}$ levels were comparable between Jinchang and Zhangye. However, nickel, copper, arsenic and selenium levels in Jinchang (nickel concentration 234.5 ng/m^3) were 82, 26, 12 and 6 times higher than in Zhangye (nickel concentration 2.8 ng/m^3), respectively. The levels of C-reactive protein, interleukin-6 and vascular endothelial growth factor were significantly higher in Jinchang. The authors conclude that specific metals may be important components responsible for PM-induced$_{2,5}$ cardiovascular effects and that reduced endothelial repair capacity may play a critical role, but the study did not assess the individual role of nickel among the 4 metals studied.

Heart rate variability

In a study published in 2011, researchers assessed the relationship between exposures to carbon and metal components of trafic-related particles and heart rate variability in 14 taxi drivers in Beijing.[37] An increase in the interquartile range (4.1 ng/m3) of nickel was associated with a 1.53 ms (95% CI: 0.14, 2.92) increase in standard deviations of normal-normal intervals.

Teratogenicity

In a study published in 2018, US researchers investigated whether prenatal residential exposure to heavy metal air pollutants is associated with an increased risk of hypospadias.[38] Data on non-syndromic hypospadias cases (n = 8981) and control patients who delivered in Texas were

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[34] Liu, Urch et al. 2018. Metals and oxidative potential in urban particulate matter influence systemic inflammatory and neural biomarkers: A controlled exposure study, Environ Int. 121(Pt 2): 1331-1340.

[35] Zanobetti, Coull, et al, Ambient Particle Components and Newborn Blood Pressure in Project Viva, J Am Heart Assoc. 2021;10:e016935. DOI: 10.1161/JAHA.120.016935

[36] Niu J, Liberda EN, Qu S, Guo X, Li X, et al. (2013) The Role of Metal Components in the Cardiovascular Effects of PM2.5. PLoS ONE 8(12): e83782. doi:10.1371/journal.pone.0083782

[37] Wu, Deng et al, Exposures to PM2.5 components and heart rate variability in taxi drivers around the Beijing 2008 Olympic Games, Science of the Total Environment 409 (2011) 2478-2485.

[38] White, Kovar et al, Hypospadias Risk from Maternal Residential Exposure to Heavy Metal Hazardous Air Pollutants, Int. J. Environ. Res. Public Health 2019, 16, 930; doi:10.3390/ijerph16060930

obtained from the Texas Birth Defects Registry and matched 1:10 by year of birth. Nickel levels ranged from 0.065 ng/m^3 to 29 ng/m^3. Cadmium, mercury, and nickel showed a significant inverted "U" shape association, with significant associations in the medium and medium-high exposure quintiles, but not in the medium-low and high exposure quintiles.

Mortality

A Canadian study conducted in 2000 assessed the impact of different components of fine particulate matter in air pollution in 8 Canadian cities.[39] The average level of nickel in $PM_{2.5}$ in these cities was 1.6 ng/m^3. The researchers found a statistically significant positive association between an increase in nickel concentration in PM and non-accidental mortality.

A European study, published in 2022 and conducted on about 27 million people representing more than 240 million person-years, reported that nickel in ambient air was significantly associated with natural mortality with a relative risk of 1.024 per 1 ng/m^3 nickel in the single exposure model, although this association did not persist after adjustment for $PM_{2.5}$ or NO_2.[40] Nickel concentrations in PM varied$_{2,5}$ between countries (or cities), from 0.4 ng/m^3 for Switzerland to 1.8 ng/m^3 for Rome.

In a study published in 2006, researchers examined the associations between 16 elements of PM_{10} and mortality for two population-based studies: the National Mortality and Morbidity Air Pollution Study (NMMAPS) and Hong Kong.[41] In the NMMAPS study, daily mortality rates in 60 US cities were significantly associated with average nickel and vanadium, but not with the other elements measured. The US national average nickel concentration reported in the study was 1.9 ng/m^3.

Animal studies

Cardiovascular system

A study published in 2011 examined the long-term cardiovascular effect of inhaled nickel nano-hydroxide (nano-NiH) in atherosclerosis-prone mice at a dose consistent with human occupational exposure scenarios.[42] Inhaled nano-NiH induced significative oxidative stress and inflammation in lung and extrapulmonary organs, indicated by upregulated mRNA levels of selected antioxidant enzyme genes and inflammatory cytokines; increased mitochondrial DNA damage in the aorta; significative signs of inflammation in the fluid of bronchoalveolar lavage; changes in lung histopathology; and induction of the acute phase response. In addition, after 5-month exposures, nano-NiH exacerbated the progression of atherosclerosis in mice.

According to the researchers, their results clearly demonstrate that long-term exposure to inhaled nano-NiH can induce oxidative stress and inflammation, not only in the lungs but also in the cardiovascular system, and that this stress and inflammation may ultimately contribute to the progression of atherosclerosis in mice.

[39] Burnett, Brook et al, 2000. Association between particulate- and gas-phase components of urban air pollution and daily mortality in eight Canadian cities, Inhalation Toxicology, 12 (Spp. 4): 15-39.
[40] Rodopoulou, Stafoggia et al, Long-term exposure to fine particle elemental components and mortality in Europe: Results from six European administrative cohorts with the ELAPSE project, Science of the Total Environment 809, 2022, 152205
[41] Lippmann, Ito et al, Cardiovascular Effects of Nickel in Ambient Air, Environ Health Perspect 114:1662-1669 (2006). doi:10.1289/ehp.9150 available via http://dx.doi.org/
[42] Kang, Gillespie et al, Long-term inhalation exposure to nickel nanoparticles exacerbated atherosclerosis in a susceptible mouse model, 2011, Environmental Health Perspectives, Vol 119, number 2, 176-181.

In a study published in 2006, mice were exposed to concentrated fine particles containing an average concentration of 43 ng/m^3 nickel.[43] Electrocardiographic measurements showed that nickel was significantly associated with acute changes in heart rate and its variability.

Central nervous system

In a study published in 2012, US researchers investigated the possibility that air pollution may contribute to the risk of Alzheimer's disease by exposing mice to a standard air pollution modelling system using an atmosphere enriched with nickel nanoparticles for 3 hours.[44] Mice exposed to air pollution showed a 72-129% increase in brain levels of both amyloid-β peptides Aβ40 and Aβ42, as well as Aβ42/40 (p.<0.01). The researchers commented that the changes observed were dramatic, rapid and unexpected. In their view, human Aβ is more pleasant than murine Aβ, so it is conceivable that the effect on Aβ levels in the human brain is even greater.

In a study published in 2018, US researchers exposed rats to three types of fine particles in Los Angeles air ($PM_{2.5}$: 12 ng/m^3 nickel concentration, $PM_{2.5\text{-}10}$: 2.5 ng/m^3 nickel concentration and ultrafine particles: 5.3 ng/m^3 nickel concentration).[45] $PM_{2.5\text{-}10}$ exposures triggered the expression of the early growth response gene 2 (EGR2), genes encoding inflammatory cytokine pathways (IL13-Rα1 and IL-16) and the oncogene RAC1. The up-regulation of the genes occurred only in the brains of rats exposed to $PM_{2.5\text{-}10}$ and correlated with brain nickel accumulation.

In a study published in 2019, rats were exposed to nickel oxide nanoparticles (NiO-NP) by inhalation at 0.23 ± 0.01 mg/m^3 for 4 h per day, 5 times per week, for up to 10 months.[46] The rat organism responded to this impact by changes in the cytological characteristics and certain biochemical characteristics of the bronchoalveolar lavage fluid, as well as by a paradoxically slight pulmonary pathology associated with a rather low chronic retention of nanoparticles in the lungs. There were various manifestations of systemic toxicity, including liver and kidney damage; a probable allergic syndrome as indicated by some cytological signs; transient stimulation of erythropoiesis; and some transfer of nanoparticles from the nasal mucosa along the olfactory tract, causing damage to the corresponding structures in the brain. Against a picture of mild to moderate chronic nickel toxicity, its in vivo genotoxic effet assessed by the degree of DNA fragmentation in nucleated blood cells (RAPD assay) was pronounced, tending to increase with the duration of the exposure period.

Pulmonary system

In a study published in 2022, researchers explored the interaction between the lung microbiome and inflammatory responses in rats exposed to nickel oxide nanoparticles (NiO NPs). [47] These nanoparticles are highly redox active. They can cause acute and chronic inflammation in the lungs of rats. NiO NPs were instilled intratracheally in rats. NiO nanoparticles provoked a neutrophilic and lymphocytic inflammatory response in the lung. It was also observed that exposure to NiO

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[43] Lippmann, Ito et al, Cardiovascular Effects of Nickel in Ambient Air, Environ Health Perspect 114:1662-1669 (2006). doi:10.1289/ehp.9150 available via http://dx.doi.org/

[44] Kim SH, Knight EM, Saunders EL et al (2012) Rapid doubling of Alzheimer's amyloid-β40 and 42 levels in brains of mice exposed to a nickel nanoparticle model of air pollution [v1; ref status: indexed, http://f1000r.es/T5Rxeo] F1000Research 2012, 1:70 (doi: 10.12688/f1000research.1-70.v1)

[45] Ljubimova, Braubach et al, Coarse particulate matter (PM2.5-10) in Los Angeles Basin air induces expression of inflammation and cancer biomarkers in rat brains, SCIENTIFIC REPORTS | (2018) 8:5708 | DOI:10.1038/s41598-018-23885-3

[46] Sutunkova, Solovyeva et al, Toxic Effects of Low-Level Long-Term Inhalation Exposures of Rats to Nickel Oxide Nanoparticles, Int. J. Mol. Sci. 2019, 20, 1778; doi:10.3390/ijms20071778.

[47] Jeong, Exposure to Nickel Oxide Nanoparticles Induces Acute and Chronic Inflammatory Responses in Rat Lungs and Perturbs the Lung Microbiome, Int. J. Environ. Res. Public Health 2022, 19, 522. https://doi.org/10.3390/ijerph19010522

nanoparticles could modify the microbial composition of the lungs in rats. Indeed, the researchers found that more burkholderiales (proteobacteria) were present in the groups exposed to NiO nanoparticles than in the control group, one day after instillation. It is proposed that dysbiosis in the lung microbiome is associated with acute lung inflammation.

Immune system

In a study published in 2021, researchers sought to establish the LOAEL (lowest observed adverse effect level) or NOAEL (no observed adverse effect level) of nickel oxide nanoparticles in rats exposed long-term by inhalation.[48] On the basis of the majority of respiratory effects and most systemic effects assessed, they came to propose a concentration close to the LOEL, and even the NOAEL. However, the experiment revealed genotoxic and allergic effects as early as the first weeks of exposure, suggesting, in their view, that these effects have no threshold at which they can be observed. The possibility of a non-threshold character of allergic responses to toxic exposures is not discussed in the literature as much as the action of genotoxic carcinogens: this possibility is however suggested by the well-known fact that sensitisation can develop in humans under the action of very low doses of allergenic agents (nickel, in particular). They conclude that this also makes the LOAEL/NOAEL concept less definitive but does not prevent its use to establish safety standards for other (non-allergic) effects.

Although relationships have been established between properties and nanomaterial-induced acute lung inflammation, the effects of properties on other responses, such as exacerbation of respiratory allergy, have been less frequently explored. In 2019, researchers evaluated the role of fine and ultrafine nickel oxide (NiO) particles in modulating allergy to ovalbumin in a mouse model.[49] In mice allergic to albumin, exposure to NiO was associated with elevated circulating total IgE levels. The authors conclude that, since the toxic effects of nanomaterials are strongly dependent on the biochemical properties of their environment, the alteration of the chemistry of the airways of asthmatics (diseased tissues) may involve different toxicity mechanisms than those of the airways of non-asthmatics (healthy tissues).

Synergy with other pollutants

In a study published in 2001, rats were exposed to aerosols of nickel, vanadium or nickel and vanadium for 6 hours per day for 4 days.[50] Even at the highest concentration, vanadium did not induce significant changes in heart rate or body temperature. Nickel induced delayed bradycardia, hypothermia and arrhythmogenesis at concentrations > 1.2 mg/m^3. When combined, nickel and vanadium produced delayed effects observable at 0.5 mg/m^3 and potentiated responses at 1.3 mg/m^3, greater than those produced by the highest concentration of Ni (2.1 mg/m^3). These results indicate a possible synergistic relationship between inhaled nickel and vanadium and provide insight into potential interactions regarding the toxicity of metals associated with particulate matter.

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[48] Katsnelson, Looking for the LOAEL or NOAEL Concentration of Nickel-Oxide Nanoparticles in a Long-Term Inhalation Exposure of Rats, Int. J. Mol. Sci. 2021, 22, 416. https://doi.org/10.3390/ijms22010416
[49] Roach, Surface area- and mass-based comparison of fine and ultrafine nickel oxide lung toxicity and augmentation of allergic response in an ovalbumin asthma model, Inhal Toxicol. 2019 July; 31(8): 299-324. doi:10.1080/08958378.2019.1680775
[50] Campen, Nolan et al, Cardiovascular and Thermoregulatory Effects of Inhaled PM-Associated Transition Metals: A Potential Interaction between Nickel and Vanadium Sulfate, TOXICOLOGICAL SCIENCES 64, 243-252 (2001).

Cytological studies

Genotoxicity

Genotoxicity is an important toxicological parameter because of its link to diseases such as cancer. Therefore, a better understanding of genotoxicity and the underlying mechanisms is needed to assess the risk associated with exposure to nanoparticles (NPs). The objective of a study published in 2018 was to conduct a thorough investigation of the genotoxicity of nickel and nickel oxide and nickel chloride NPs in human bronchial epithelial cells BEAS-2B.[51] Despite differences in cell uptake, all exposures (NiO NPs, Ni NPs and NiCl2) caused chromosomal damage. In addition, NiO nanoparticles were the most potent in causing DNA strand breaks.

Nervous system cells

Several reports indicate that the brain is another target affected by exposure to fine particles. In a study published in 2007, the cellular and genomic response of immortalised mouse microglia (BV2) was examined in response to fine (≤ 2.5 µm) concentrated ambient particles (CAP) collected in Tuxedo, New York.[52] CAP samples were labelled as high power (HP) or low power (LP) based on their stimulation of nuclear factor (NF)-κ B activity in human bronchial epithelial cells. Compositional analysis of these samples, carried out during their initial collection, indicated a strong correlation between HP PACs and the presence of nickel and vanadium. Their results suggest that HP-ACPs, which contained higher levels of nickel and vanadium than LP-ACPs, appeared to be more inflammatory and selectively regulated the expression of inflammatory and innate immune pathways in BV2 microglia.

Immunotoxicity

A study attempted to elucidate the cytotoxicity and genotoxic capacity of nickel oxide (NiO) nanoparticles (NPs) on human peripheral blood lymphocytes.[53] It was concluded that the preliminary mechanism of cytotoxicity of NiO-NPs on lymphocytes was oxidative stress-mediated apoptosis and DNA damage.

Listed nickel standards

European standard

To put the scientific approach that led to the annual nickel standard of 20 ng/m^3 adopted by the European Union into perspective, we will refer to the European Commission's position statement published in 2000[54] and the opinion of the Scientific Committee on Toxicity, Ecotoxicity and the Environment (SCTE). This perspective on the European approach will support our position on the Quebec standard.

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[51] Di Bucchianico, Gliga et al, Calcium-dependent cyto- and genotoxicity of nickel metal and nickel oxide nanoparticles in human lung cells, Particle and Fibre Toxicology (2018) 15:32 https://doi.org/10.1186/s12989-018-0268-y
[52] Sama, Long et al, The Cellular and Genomic Response of an Immortalized Microglia Cell Line (BV2) to Concentrated Ambient Particulate Matter, International Forum for Respiratory Research, Volume 19, 2007 - Issue 13: 1079-1087, DOI: 10.1080/08958370701628721
[53] Dumal et al, In vitro genotoxicity assessment of nickel(II) oxide nanoparticles on lymphocytes of human peripheral blood, J. Appl Toxicol, 39 (2019), pp. 955-965
[54] Ambient air pollution by AS, CD and NI compounds. Position Paper, 2000, European commission, 318 pages. https://ec.europa.eu/environment/air/pdf/pp_as_cd_ni.pdf

Average nickel concentrations observed in Europe

In remote areas, annual average concentrations of nickel in air are in the order of 1 ng/m³ or less and in rural areas 0.4-2 ng/m³.[55] In urban areas, 1.4-13 ng/m³ seems to be a realistic range. In industrial areas of most European Community (EC) countries, nickel concentrations vary between 10 and 50 ng/m³. However, in highly industrialised areas, concentrations up to 100 ng/m³ are possible.

Nickel speciation

The limited number of speciation measurements in ambient air suggests that oxidised nickel is the main fraction (about 50%), followed by soluble nickel compounds (20-40%) and smaller portions of metallic and sulfide nickel (5-8%).[56] Sulfide nickel ores are mainly associated with nickel-bearing pyrrhotite (FeS_{78}), pentlandite $(Ni.Fe)_9S_8$ and chalcopyrite ($CuFeS_2$). The main sulfide deposits are found in Canada, the former Soviet Union, the Republic of South Africa, Australia, Zimbabwe, and Finland.

Establishing the limit value

According to the European Commission's position paper, non-cancerous health effects are allergic skin reactions (generally not caused by inhalation), effects on the respiratory tract, the immune and defence system and on endocrine regulation.[57] As well-documented human data are scarce, animal data must be used for the assessment of non-cancer effects.

The WHO gives a unit risk of $3.8 \times 10^{-4}(\mu g/m^3)^{-1}$, while the US EPA has estimated that the lifetime cancer risk from exposure to nickel refinery dust is $2.4 \times 10^{-4}(\mu g/m^3)^{-1}$. These estimates lead to a concentration range of 2.6 - 4 ng/m³, when extrapolated to a lifetime excess risk of one in a million.

Taking into account the likely overestimation of risk due to the fact that the limit value will be based on total nickel, i.e. without speciation, and other uncertainties, a limit value between 10 and 50 ng/m³ on an annual basis, derived from non-cancer effects, was considered to be sufficiently protective also against cancer effects. The majority of the working group proposed a limit value at the lower end of this range.

Taking into account the possible overestimation of risk by applying linear extrapolation and the apparent difference between nickel compounds in their carcinogenic activity, it is considered by the World Health Organisation, one of the members of the European Commission's working group, that the lower end of the range (10 ng Ni/m³) is sufficiently protective of the general population from the carcinogenic effects of nickel compounds in ambient air.

Another member of the working group, the European Environmental Bureau (EEB), proposes to take particular account of the precautionary principle that levels of possible genotoxic carcinogens should not be allowed to increase, and to use approximately the upper limit of the urban background values of 10 ng Ni/m³ as a limit value.

In the same position paper, the industrial members of the working group did not agree with the recommendation of 10 ng/m³ as a limit value. In their view, the risk should be reduced by the

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[55] Ibid.
[56] Ibid.
[57] Ibid.

maximum relative concentration of nickel subsulfide (i.e. ~30%) in ambient air. The industry members propose 50 ng/m^3. The position paper reports that it was discussed in the working group, without unanimity, that according to the precautionary principle, current concentrations of carcinogenic compounds in ambient air should not increase. No consensus was reached. EEB and WHO maintained their proposal of 10 ng/m^3, and industry its proposal of 50 ng/m^3.

In an opinion on the position paper, the European Commission's SCTEE (Scientific Committee on Toxicity, Ecotoxicity and the Environment), which served from 1997 to 2004, supported the WHO recommendation of a unit risk of 3.8 x 10^{-4} (mg Ni/m^3) based^{-1} on the excess risk observed in the Falconbridge nickel worker cohort.[58] This corresponds to concentrations of 25 ng Ni/m^3 and 2.5 ng Ni/m^3 for increased lifetime risks of 1:100,000 and 1:1,000,000, respectively. In their view, these estimates are inherently conservative, given the linear extrapolation over several orders of magnitude from the observed excess risk in exposed humans. In addition, there are considerable differences in the carcinogenic potency of the different nickel species in ambient air, with the most potent sulphuric nickel accounting for only 10% of the sum of nickel species in air, based on the limited amount of data available. The CSTEE therefore concludes that the proposed limit value of 20 ng Ni/m^3 for non-carcinogenic effects is also likely to provide reasonable protection of the general population against the carcinogenic effects of nickel compounds in ambient air.

[58] Opinion on: Position Paper on Ambient Air Pollution by Nickel Compounds. Final Version October 2000. Opinion expressed at the 22nd CSTEE plenary meeting, Brussels, 6/7 March 2001.

American standards

Environmental Protection Agency standards based on estimated cancer risk

The US Environmental Protection Agency (EPA) has classified nickel refinery dust and nickel subsulfide as a Group A human carcinogen.[59] The EPA uses mathematical models, based on animal studies, to estimate the likelihood of a person developing cancer by breathing air containing a given concentration of a chemical. The EPA has calculated a unit inhalation risk estimate of 2.4×10^{-4} $(\mu g/m^3)^{-1}$ for nickel refinery dust. The EPA estimates that if an individual continuously breathed air containing nickel refinery dust at an average of 4 ng/m^3 throughout his or her lifetime, that person would theoretically have no more than a one-in-a-million chance of developing cancer as a direct result of breathing air containing this chemical. Similarly, the EPA estimates that breathing air containing 40 ng/m^3 would not increase the risk of developing cancer by more than one in a hundred thousand, and that air containing 400 ng/m^3 would not increase the risk of developing cancer by more than one in ten thousand.

For nickel subsulfide, the EPA calculated a unit inhalation risk estimate of 4.8×10^{-4} $(\mu g/m^3)^{-1}$. The EPA estimates that if a person were to breathe air containing this nickel compound continuously at an average of 2 ng/m^3 throughout their lifetime, that person would theoretically have no more than a one in a million chance of developing cancer as a direct result of breathing air containing this chemical. Similarly, the EPA estimates that permanently breathing air containing 20 ng/m^3 would not increase the risk of developing cancer by more than one in one hundred thousand, and that air containing 200 ng/m^3 would not increase the risk of developing cancer by more than one in ten thousand.

California Office of Environmental Health Hazard Assessment (OEHHA) Noncancer Reference Exposure Levels

Average nickel concentrations observed in California

The annual average ambient air concentration of nickel measured by the air monitoring network operated by the California Air Resources Board and local air districts in 2002 was 4.5 ± 4.1 SD ng/m^3.[60] This value was quite similar to values reported for the previous years, 1992 to 2001. Data from the South Coast airshed showed average concentrations of nickel in total suspended particulate matter of about 6 ng/m^3. The highest individual area was West Long Beach, at about 11 ng/m^3, which may be a result of increased shipping activity in the ports, as nickel is naturally present in the fuel used in ships. In general, concentrations ranged from 2 to 9 ng Ni/m^3.

Noncancer Reference Exposure Levels

The California Office of Environmental Health Hazard Assessment (OEHHA) published Noncancer RELs (Reference Exposure Levels) for nickel in 2012 (Table 1).[61]

[59] https://www.epa.gov/sites/default/files/2016-09/documents/nickle-compounds.pdf
[60] https://oehha.ca.gov/media/downloads/crnr/032312nirelfinal.pdf
[61] Ibid.

Table 1. OEHHA's Noncancer RELs for nickel

1.1 Acute Toxicity (for a 1-hour exposure)	
Inhalation reference exposure level	**0.2 µg Ni/m³**
Critical effect(s)	Immune system
Hazard Index target(s)	Immune system
1.2 8-Hour REL (for repeated 8-hour exposures)	
Inhalation reference exposure level	**0.06 µg Ni/m³**
Critical effect(s)	Lung lesions, immunotoxicity
Hazard Index target(s)	Respiratory system; immune system
1.3 Chronic REL Nickel and Nickel Compounds (except NiO)	
Inhalation reference exposure level	**0.014 µg Ni/m³**
Critical effect(s)	Lung, nasal epithelial and lymphatic pathology in male and female rats
Hazard index target(s)	Respiratory system; hematopoietic system
1.4 Chronic REL Nickel Oxide	
Inhalation reference exposure level	**0.02 µg Ni/m³**
Critical effect(s)	Lung pathology in male and female mice
Hazard index target(s)	Respiratory system

Acute exposure

The 8-hour REL is based on respiratory and immunological effects. The 8-hour REL uses the NTP sodium sulphate inhalation study in rats[62] as a critical study and the Graham et al (1978) study in mice[63] with nickel chloride as a supporting study.

Chronic exposure

The two cRELs for nickel and nickel compounds (except nickel oxide) and for nickel oxide are based on the pulmonary toxicity observed in the National Toxicology Program (NTP) studies. [64][65] For pulmonary toxicity, nickel oxide is considered less toxic than nickel sulphate or nickel subsulfide, which are considered equivalent in terms of respiratory effects.

Data robustness and limitations

In its report, the OEHHA commented on the strength and limitations of the data for the development of Noncancer cRELs.[66] According to OEHHA:

> The strength of the data includes the availability of controlled lifetime inhalation studies in multiple species at multiple exposure concentrations and with adequate histopathological analysis, as well as

[62] Toxicology and carcinogenesis studies of nickel sulfate hexahydrate in F344/N rats and B6C3F mice, 1996, U.S. Department of health and Human Services, National Institute of Health, National Toxicology Program, Technical Report Series, No 454.

[63] Graham, J., Miller, F., Daniels, M., Payne, E., Gardner, D. 1978. Influence of cadmium, nickel, and chromium on primary immunity in mice. Environmental research, 16(1-3), 77-87.

[64] Toxicology and carcinogenesis studies of nickel sulfate hexahydrate in F344/N rats and B6C3F mice, 1996, U.S. Department of health and Human Services, National Institute of Health, National Toxicology Program, Technical Report Series, No 454.

[65] Toxicology and carcinogenesis studies of nickel oxide in F344/N rats and B6C3F mice, 1996, U.S. Department of health and Human Services, National Institute of Health, National Toxicology Program, Technical Report Series, No 451.

[66] Nickel Reference Exposure Levels, OFFICE OF ENVIRONMENTAL HEALTH HAZARD ASSESSMENT, 2012, 193 pages.

the observation of a NOAEL (No-Observed-Adverse-Effect Level). The main areas of uncertainty are the lack of adequate human exposure data and the absence of lifetime toxicity studies in any species other than rodents. The toxicological response to various inhaled nickel compounds in children versus adults is also an area of uncertainty addressed by a larger uncertainty factor for intra-individual variation. Nickel targets the immune system and lung, which are likely to be more sensitive systems and organs in exposed infants and children.

Warning for children

OEHHA adds a warning section to the effect that:

> NICKEL IS A TOXIC AIR CONTAMINANT THAT HAS A DISPROPORTIONATE IMPACT ON CHILDREN. There is a potential for exposure to nickel and nickel compounds due to its widespread presence and many uses. Nickel is a minor component of airborne particles (PM) and may play a role in the toxicity of PM. Adverse effects of nickel compounds on the respiratory and immune systems (including asthma), as well as increased perinatal mortality and reduced birth weight observed in animal reproductive toxicity studies, are among the types of effects leading to the potential for differential impacts on infants and children. OEHHA therefore recommends that nickel be identified as a toxic air contaminant, which may have a disproportionate impact on children, pursuant to Health and Safety Code Section 39669.5(c).

Ontario Standard

In the Toxicological Review of the Nickel Industry Regulatory Framework for Ambient Air,[67] it is stated for Ontario for the annual standard for nickel in PM_{10} that:

> The ambient air quality criterion of 0.02 µg/m^3 for nickel and its compounds in the PM_{10} size fraction was essentially determined by considering the approach used by the European Union (European Commission (EC, 2001)) and its expert committee the Scientific Committee on Toxicity, Ecotoxicity and the Environment (CSTEE, 2001)). The limit value of 20 ng/m^3 (annual average) should also protect against the effects of the subsulfide forms of nickel (NiS_{32}) according to the Ontario Ministry of the Environment, considering its low percentage in the ambient air. Specifically, the overall province-wide nickel speciation results show no detectable levels of nickel subsulfide. Even with low levels of nickel subsulfide (≈ 10% of total nickel), the limit value of 20 ng/m^3 was considered to be consistent with the concentration associated with acceptable risk derived from the WHO unit risk (1 in 100,000 cases that could be considered acceptable by the major agencies for exposure to 25 ng/m^3)...In sum, the Ontario Ministry of the Environment considered it reasonable to use the EU derived limit value of 20 ng/m^3 as the AQAA (annual average) considering the speciation in air and toxicity aspects of the different forms of nickel.

And it says for Ontario for the 24-hour nickel standard in PM_{10} that:

> Finally, in order to convert an ambient air quality criterion expressed as an annual average to an ambient air quality criterion expressed as a 24-hour average, the Ministry generally uses a conversion factor of 5. This factor, which is not specific to nickel, is based on empirical monitoring data, ratios of observed concentrations for different averaging times and meteorological considerations.

[67] Bouchard, Toxicological review of the regulatory framework for the nickel industry for the ambient air component, 2018, 104 pages.

Western Australia Guide Value

According to the Executive[68] Summary of the Toxicological Review of the Nickel Industry Regulatory Framework for Ambient Air:

> ... Western Australia is based on the annual average value of 3 ng/m^3 that should not be exceeded, derived from the cancer risk calculated by WHO (2000) from lung cancer data for refinery workers at the time (concentration of 2.5 ng/m^3 associated with a 1 in 1,000,000 chance of developing lung cancer).

A look at Quebec and the proposed standard

Level of risk considered negligible by the MELCC

According to the MELCC's *Cadre de détermination et d'application* des *Normes et critères de qualité de l'atmosphère du Québec* published in 2017, the level of negligible risk for a contaminant presenting an effect on human health can be interpreted as follows:[69]

- Threshold substance: for substances causing an effect for which the existence of a physiological threshold of occurrence is assumed, the application of uncertainty factors (or an equivalent method) leads to the determination of concentrations that do not cause an effect.
- Non-threshold substance: For some substances causing a major effect (e.g. some carcinogenic compounds), it is assumed that the probability of occurrence of an effect increases from the "zero" exposure dose. It is therefore not possible to determine a no-effect concentration. In these cases, the negligible risk level for the occurrence of the effect is set at one additional case per million people exposed over a lifetime.

MELCC Sustainability Principles

We would like to remind you of the MELCC's sustainable development principles that we consider relevant to the revision of the nickel standard: [70]

> (a) "Health and quality of life": People, the protection of their health and the improvement of their quality of life are at the centre of sustainable development concerns. People have a right to a healthy and productive life in harmony with nature.
> (c) "environmental protection": to achieve sustainable development, environmental protection must be an integral part of the development process.
> (i) 'prevention': where a risk is known, preventive, mitigating and remedial actions should be taken, primarily at source.

[68] Bouchard, Toxicological review of the regulatory framework for the nickel industry for the ambient air component - Executive summary, 2018, 7 pages.
[69] MINISTÈRE DU DÉVELOPPEMENT DURABLE, DE L'ENVIRONNEMENT ET DE LA LUTTE CONTRE LES CHANGEMENTS CLIMATIQUES (2017). Normes et critères de qualité de l'atmosphère du Québec : Cadre de détermination et d'application, Québec, Direction générale du suivi de l'état de l'environnement, ISBN: 978-2-550-79483-7 (PDF), 18 p. [Online]. http://www.mddelcc.gouv.qc.ca/air/criteres/index.htm
[70] Sustainable Development Act https://www.legisquebec.gouv.qc.ca/fr/document/lc/D-8.1.1

(j) 'precaution' means that where there are threats of serious or irreversible damage, lack of full scientific certainty shall not be used as a reason for postponing cost-effective measures to prevent environmental degradation.
(n) "responsible production and consumption": changes in production and consumption patterns are needed to make them more sustainable and socially and environmentally responsible, inter alia by adopting an eco-efficient approach, avoiding waste and optimising the use of resources.
(o) "polluter pays": those who generate pollution or whose actions otherwise degrade the environment must bear their share of the costs of measures to prevent, reduce and control damage to environmental quality.
(p) 'cost internalisation': the value of goods and services should reflect the full costs to society over their entire life cycle, from conception to consumption and final disposal.

MELCC proposal to amend the Quebec standard

The MELCC wants to replace the current Quebec standard of 14 ng/m ^{3}24-hr PM_{10} with a standard of 70 ng/m ^{3}24-hr PM $_{10}$and adopt a standard of 20 ng/year^{3} PM_{10}.

The MELCC Nickel Air Quality Standard Fact Sheet states:

NICKEL SPECIATION
According to Environment Canada (1994), nickel can be present in the environment in several forms, including oxygenated nickel compounds (nickel monoxide, nickel copper oxide, silicate nickel oxides, complex oxides), sulphur compounds (including trinickel disulfide), and soluble compounds (mainly trinickel sulphate and dichloride).
As most of the nickel in urban air comes from the combustion of fossil fuels (ATSDR, 2005), it is likely that sulphates are on average the most common species of nickel in urban areas (INERIS, 2006). However, in the NTP study (1996), laboratory animals were exposed to nickel sulphate hexahydrate, which is the basis for the daily air quality criterion.
In addition, nickel analysis in Quebec air is performed on samples of total suspended particulate matter (TSP) or particles smaller than 10 microns (PM_{10}). The filters containing the particles are digested in a solution of nitric acid and hydrochloric acid, and the extracted nickel is quantified by ICP-MS (U.S. EPA, 1999). This analytical procedure does not distinguish between the different chemical species of nickel.

DETERMINATION OF NO HARM CONCENTRATION (NHC-i) 1 YEAR
Studies by Goodman et al. (2009 and 2011) suggest that in order to exert a genotoxic effect, the Ni^{2+} ion must reach the nucleus of the cell, allowing it to interact with DNA. Sulphur compounds and nickel oxides would therefore be more likely to cause genotoxic effects, as they would have a higher bioavailability of the Ni^{2+} ion in the nucleus. For soluble compounds, which have a lower bioavailability of the Ni^{2} ion in the nucleus, the mechanisms of action would be mainly non-genotoxic. A criterion based on a linear incremental cancer risk should therefore apply only to sulphuric nickel compounds and oxides, whereas a threshold approach should be considered for soluble compounds and metallic nickel.

Currently, no data on nickel speciation in ambient air in Quebec or in emissions from sources is available. However, to establish their cancer risks, the United States Environmental Protection Agency (U.S. EPA) and the World Health Organization (WHO) have considered studies in which the percentages of nickel subsulfide are very high compared to what would be expected in Quebec ambient air, even in the vicinity of sources emitting nickel. Since nickel subsulfide has a higher genotoxic potential than most forms of nickel found in ambient air, the use of the U.S. EPA and WHO unit risks may lead to an overestimation of risk. The TCEQ unit risk was used as the threshold for

> establishing a cancer risk since special care was taken to select studies with a lower proportion of nickel subsulfide. Since the exact proportion of nickel subsulfide in the air in Québec is not known and since this percentage could vary in the vicinity of certain potential sources, no correction is made to this value in order to estimate a unit risk based on the concentrations of nickel subsulfide in the ambient air.

In the Toxicological Review of the Nickel Industry Regulatory Framework for the Ambient Air Component,[71] it states

> The MDDELCC (2013) mentions that the standard should be applied to all nickel compounds, including nickel oxides, nickel sulfides and soluble compounds (nickel sulphate and nickel chloride). It also mentions that the sulphate form is probably the most abundant form in air, consistent with what has been reported by other agencies (OEHHA, 2012; CSTEE, 2001).

Thus, both the MELCC's Air Quality Standard Data Sheet on Nickel and the Toxicological Review of the Nickel Industry Regulatory Framework for Ambient[72] Air estimate that Québec's ambient air has a composition similar to that of Europe and Ontario, with a high proportion of nickel sulphate. This proportion is probably true throughout Quebec, except in the CLSC Basse-Ville/Limoilou-Vanier area, where nickel iron sulfide ($NiFeS_{998}$) **(pentlandite transshipped by the Port of Quebec) accounts for almost 100% of the cocktail, as demonstrated by the MELCC[73]'s 2013 report on the *origin of elevated nickel concentrations in the ambient air in Limoilou.***

Large excerpts from this report are inserted under the section *Portrait de la population québécoise touchée par la pollution au nickel*. We are surprised that neither the Fact Sheet nor the Toxicology Review refers to this nickel speciation study done in Quebec and that the Fact Sheet states that currently, no data on nickel speciation in ambient air in Quebec or in emissions from sources is available.

Carcinogenic effects of pentlandite

Pentlandite is a brownish-yellow mineral consisting of a sulfide of iron and nickel in a cubic crystalline form.[74] Very few studies have been published on the toxicity of this nickel-iron sulfide. However, pentlandite has the potential to be carcinogenic as a statistically significant increase in mortality from lung cancer has been reported in pentlandite miners in Ontario (Table 2, next page).[75]

[71] Bouchard, Toxicological review of the regulatory framework for the nickel industry for the ambient air component, 2018, 104 pages.
[72] Ibid.
[73] Walsh and Brière, Origine des concentrations élevées de nickel dans l'air ambiant à Limoilou, MELCC, 2013, 21 pages.
[74] https://www.collinsdictionary.com/us/dictionary/english/pentlandite
[75] ICNCM, Report of the international committee on nickel carcinogenesis in man. Final report. 1990, Program Resources, Inc, Research Triangle Park, NC (USA). Scand J Work Environ Health 1990;16(1):1-82.

Table 2. Lung cancer mortality in Ontario pentlandite miners with 15 or more years since first exposure

Mine	Number of minors	Duration of exposure (years)	Observed number of deaths	Estimated number of deaths based on mortality rates in Ontario	Standardised mortality ratio	Value of P
Falconbridge, Ontario	4 656	≥ 5	46	29.07	158	<0.01
INCO (Ontario)	23 452	≥ 25	129	96.29	134	<0.001

Based on another Ontario study, [76]some have concluded that this excess lung cancer mortality is consistent with that observed for other hard rock and non-nickel miners and that this excess cancer is not caused by nickel per se but rather by the presence of fine particles. However, when we look closely at this Ontario study, we discover that there is a methodological flaw. The group of nickel miners (presumably pentlandite miners) was in fact composed of nickel or copper miners. Since copper is not a known carcinogen,[77] the presence of copper miners potentially skewed the results for nickel miners.

Some people refer to a 1992 study on hamsters to claim that pentlandite is not carcinogenic.[78] However, in our opinion, this study must be considered invalid because of a major methodological flaw. The study used two groups of hamsters: a group exposed to pentlandite (the compound of interest), and a control group exposed to nickel subsulfide of the $NiS2_3$ type, which is already recognised as a carcinogen. However, the control group did not develop cancer significantly, demonstrating that the animal model used for the study was not adequate to reproduce the desired effect. This study cannot therefore be used as a reference point to justify the safety of pentlandite. It is recognised that rodent species differ in their sensitivity to the carcinogenic effects of nickel compounds, with hamsters and mice being much less sensitive than rats.[79] In this study, it is notable that pentlandite remained in the lung nine times longer than the positive control nickel subsulfide (NiS_{32}).[80] Some have associated the increased carcinogenicity of nickel sulfides with their relative insolubility compared to the more soluble nickel sulphate.[81] Soluble nickel particles are dissolved in mucus and nickel ions are rapidly removed by ciliary transport. In contrast, less soluble nickel particles can enter lung epithelial cells by phagocytosis where they are slowly dissolved, providing a continuous source of genotoxic nickel.

[76] Muller, J., et al, Study of Mortality of Ontario Miners 1955-1977. Part I. 1983, Ontario Ministry of Labour, Ontario Workers' Compensation Board, Atomic Energy Control Board of Canada.
[77] https://www.der.wa.gov.au/images/documents/our-work/consultation/air%20emissions/Guideline%20-%20Air%20emissions.pdf
[78] Muhle, H., et al, Chronic effects of intratracheally instilled nickel-containing particles in hamsters. Advances in environmental science and technology, 1992. 25: p. 467-479.
[79] https://www.sciencedirect.com/topics/agricultural-and-biological-sciences/nickel-sulfide
[80] http://www.vale.com/PT/business/mining/nickel/product-safety-information/SafetyDataSheets/VBN%20Middlings%20CDN%20EN%20v1.pdf
[81] Schaumloffel, Nickel species: analysis and toxic effects, J. Trace Elem. Med. Biol, 26 (2012), pp. 1-6

In addition, two studies in rats reported the development of sarcomas at the site of intramuscular injection of nickel ferrosulfide $FeNiS_{44}^{+3}$.[82] The rates of sarcoma development in these rats (8/10 and 15/15) were comparable to the groups of rats injected with nickel subsulfide (8/10 and 14/14). One of the studies reported that the median latency periods were 30 weeks for nickel subsulfide, but only 16 weeks for nickel ferrosulfide. The median survival times were 39 and 32 weeks, respectively.

Critical discussion on the revised Quebec standard

For a toxic effect to be considered due to acute exposure, it is not necessary for the effects to be observed immediately. Instead, effects may be observed hours or days after acute exposure. The California Office of Environmental Health Hazard Assessment (OEHHA) has chosen to adopt the US EPA's general definition of adverse effects as "a biochemical change, functional impairment, or pathological lesion that adversely affects the performance of the whole organism, or that reduces the ability of an organism to respond to an additional challenge". The non-cancer effects assessed for standard setting are mainly immunological and respiratory effects. For these non-cancer effects, the data are based exclusively on animal models and mainly on the NTP[83] studies [84,85]in rodents (rats and mice) published 25 years ago. However, since their publication, several other studies on inhaled nickel using new diagnostic technologies have been published.

For example, recent studies published after the NTP studies, the adoption of the European standard or the establishment of the Californian RELs have reported potential effects of nickel on the cardiovascular (altered heart rate, atherosclerosis, increased blood pressure, cardiovascular hospitalisations) [86]and[87,88,89] central nervous systems (upregulation of genes in the brain, deposition of amyloid-β peptides, autism) [90] as well[91,92] as an increase in non-accidental mortality in humans [93](see section on *Health impacts of nickel*).

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[82] https://www.ncbi.nlm.nih.gov/books/NBK519249/#p257-bib309
[83] Toxicology and carcinogenesis studies of nickel oxide in F344/N rats and B6C3F mice, 1996, U.S. Department of health and Human Services, National Institute of Health, National Toxicology Program, Technical Report Series, No 451.
[84] Toxicology and carcinogenesis studies of nickel subsulfide in F344/N rats and B6C3F mice, 1996, U.S. Department of health and Human Services, National Institute of Health, National Toxicology Program, Technical Report Series, No 453.
[85] Toxicology and carcinogenesis studies of nickel sulfate hexahydrate in F344/N rats and B6C3F mice, 1996, U.S. Department of health and Human Services, National Institute of Health, National Toxicology Program, Technical Report Series, No 454.
[86] Bell ML, Ebisu K, Peng RD, Samet JM, Dominici F. Hospital admissions and chemical composition of fine particle air pollution, 2009, Am J Respir Crit Care Med, 179(12): 1115-20.
[87] Wu, Deng et al, Exposures to PM2.5 components and heart rate variability in taxi drivers around the Beijing 2008 Olympic Games, Science of the Total Environment 409 (2011) 2478-2485.
[88] Zanobetti, Coull, et al, Ambient Particle Components and Newborn Blood Pressure in Project Viva, J Am Heart Assoc. 2021;10:e016935. DOI: 10.1161/JAHA.120.016935
[89] Kang, Gillespie et al, Long-term inhalation exposure to nickel nanoparticles exacerbated atherosclerosis in a susceptible mouse model, 2011, Environmental Health Perspectives, Vol 119, number 2, 176-181.
[90] Kim SH, Knight EM, Saunders EL et al (2012) Rapid doubling of Alzheimer's amyloid-β40 and 42 levels in brains of mice exposed to a nickel nanoparticle model of air pollution [v1; ref status: indexed, http://f1000r.es/T5Rxeo] F1000Research 2012, 1:70 (doi: 10.12688/f1000research.1-70.v1)
[91] Windham, Zhang et al, Autism Spectrum Disorders in Relation to Distribution of Hazardous Air Pollutants in the San Francisco Bay Area, Environ Health Perspect 114:1438-1444 (2006). doi:10.1289/ehp.9120 available via http://dx.doi.org/
[92] Ljubimova, Braubach et al, Coarse particulate matter (PM2.5-10) in Los Angeles Basin air induces expression of inflammation and cancer biomarkers in rat brains, SCIENTIFIC REPORTS | (2018) 8:5708 | DOI:10.1038/s41598-018-23885-3
[93] Burnett, Brook et al, 2000. Association between particulate- and gas-phase components of urban air pollution and daily mortality in eight Canadian cities, Inhalation Toxicology, 12 (Spp. 4): 15-39.

It should be noted that neither rats nor mice are predisposed to atherosclerosis or Alzheimer's disease. Only a few genetically modified lines are. [94][95][96][97] The mouse (B6C3F) and rat (F344/N) lines used in the NTP studies do not appear to be susceptible to atherosclerosis or Alzheimer's disease. Furthermore, cardiac function (rhythm, blood pressure, markers of vascular inflammation, etc.) was not assessed in the NTP studies. And finally, nickel accumulation in the brain was not assessed, nor was gene activation or deposition of amyloid-β peptides.

OEHHA warns that **nickel is a toxic air contaminant that has a disproportionate impact on children**. However, the rats and mice used in the NTP studies were seven weeks old when the studies began. At this age, these rodents are pubescent and considered young adults. [98][99][100] The NTP studies cannot therefore be extrapolated to children, which is why a correction factor is included in the OEHHA REL calculation.

A potential synergy between nickel and other pollutants was not taken into account. However, a study in rats reported potential synergy between vanadium and nickel. [101] As the European Commission's position paper states, it is important to recognise that emission controls alone cannot exclude the possibility of adverse effects from the simultaneous presence of emissions from various sources, even if each source meets the emission standards.[102]

Atmospheric nickel particles belong to the category of fine particles. It is important to note that 10 to 20 years have passed since the WHO, CSTEE and OEHHA guidelines were issued. Over the past 20 years, multiple studies have led to the conclusion that very low levels of air pollutants can have a negative impact on health, so that in 2021 the World Health Organisation lowered its guidelines for the main pollutants (Table 3, next page).

[94] Paigen, Morrow et al, Variation in susceptibility to atherosclerosis among inbred strains of mice, Atherosclerosis. 1985 Oct;57(1):65-73. doi: 10.1016/0021-9150(85)90138-8. https://pubmed.ncbi.nlm.nih.gov/3841001/
[95] Kunimasa, Yoshitomi et al, High susceptibility of obese hypertensive SHRSP.Z-Lepr(fa)/IzmDmcr rats to lipid deposition in the mesenteric artery, Clin Exp Pharmacol Physiol. 2010 Nov;37(11):1102-4. doi: 10.1111/j.1440-1681.2010.05440.x
[96] Benedikz, Kloskowska and Winblad, The rat as an animal model of Alzheimer's disease, J Cell Mol Med. 2009 Jun; 13(6): 1034-1042. doi: 10.1111/j.1582-4934.2009.00781.x
[97] Jackson, Andrews et al, Does age matter? The impact of rodent age on study outcomes, Lab Anim. 2017 Apr; 51(2): 160-169. doi: 10.1177/0023677216653984
[98] Sengupta, The Laboratory Rat: Relating Its Age With Human's, Int J Prev Med. 2013 Jun; 4(6): 624-630.
[99] Adami Andreollo, Freitas dos Santos, et al, Rat's age versus human's age: what is the relationship? Arq Bras Cir Dig. Jan-Mar 2012;25(1):49-51. doi: 10.1590/s0102-67202012000100011.
[100] Dutta and Sengupta, Review article Men and mice: Relating their ages, Life Sciences, Volume 152, 1 May 2016, Pages 244-248.
[101] Campen, Nolan et al, Cardiovascular and Thermoregulatory Effects of Inhaled PM-Associated Transition Metals: A Potential Interaction between Nickel and Vanadium Sulfate, TOXICOLOGICAL SCIENCES 64, 243-252 (2001).
[102] Ambient air pollution by AS, CD and NI compounds. Position Paper, 2000, European commission, 318 pages. https://ec.europa.eu/environment/air/pdf/pp_as_cd_ni.pdf

Table 3: World Health Organization 2021 guidelines for different pollutants compared to the 2005[103] guidelines (AQG = Air Quality guidelines)

Recommended 2021 AQG levels compared to 2005 air quality guidelines

Pollutant	Averaging Time	2005 AQGs	2021 AQGs
$PM_{2.5}$, µg/m^3	Annual	10	5
	24-hour[a]	25	15
PM_{10}, µg/m^3	Annual	20	15
	24-hour[a]	50	45
O_3, µg/m^3	Peak season[b]	-	60
	8-hour[a]	100	100
NO_2, µg/m^3	Annual	40	10
	24-hour[a]	-	25
SO_2, µg/m^3	24-hour[a]	20	40
CO, mg/m^3	24-hour[a]	-	4

As stated earlier, the new WHO guideline for $_{2.5}$24-hour PM is lower than the $_{2.5}$24-hour PM standard in the MELCC's *Règlement sur l'assainissement de l'atmosphère* (RAA) (24-hour $PM_{2.5}$ at 30 µg/m^3). The RAA does not have an $_{2.5}$annual PM standard or a $_{10}$24-hour or annual PM standard, although nickel is a constituent of this category of pollutants.

[103] https://www.who.int/news-room/feature-stories/detail/what-are-the-who-air-quality-guidelines

AQME POSITIONING

In our view, **the new revised Quebec standard proposed by the MELCC is based on a fundamental error that the** composition of Quebec's ambient air is similar to that of Europe and Ontario with a high presence of nickel sulphate. The MELCC fact sheet states that no data on nickel speciation in Quebec ambient air or in source emissions is available, whereas **a 2013 MELCC report shows that, in the CLSC Basse-Ville/Limoilou-Vanier area, nickel iron sulfide ($NiFeS_{998}$) (pentlandite transshipped through the Port of Quebec) accounts for almost 100% of the cocktail**. However, the European nickel standard, the Californian RELs and the Ontario standard are based on the fact that nickel sulphate is a predominant form of nickel in the ambient air, whereas the proportion of nickel subsulfide NiS_{32} is about 10%, which is why they considered that their standards or RELs protected against both cancerous and non-cancerous effects.

The situation is different in Quebec since nickel-iron sulfide represents almost 100% of the atmospheric nickel in the population known to be most affected by nickel pollution. **Given that the main form of nickel in the air in Quebec, nickel-iron sulfide, is therefore a very little studied substance, it seems unreasonable to us to base the Quebec nickel standard on nickel sulphate.** Western Australia, which mines large quantities of nickel in the form of pentlandite, has instead chosen to adopt an annual nickel standard of 3 ng/md^3 in PM10 based on the WHO guide value for the carcinogen nickel subsulfide.

This is why we recommend an annual standard based on the WHO unit risk for cancer of 3 ng/m3 in PM_{10} in order to be consistent with the negligible risk level of the MELCC effect established at one additional case of cancer per million people exposed over a lifetime. This standard seems realistic to us considering the level of nickel observed in the PM_{10} of several Quebec and Canadian cities. For the 24-hour standard, we recommend multiplying the annual standard by a conversion factor of 5, as used by the Ontario Ministry of the Environment,[104] which would result in the adoption of a standard of 15 ng/m ^{3}24-hour in PM10, or roughly the same as the standard before revision of 14 ng/m ^{3}24-hour in PM_{10}.

We would like to remind you that the adoption of standards for various air pollutants is intended to protect the health and life of the population and that **the Quebec government has a moral duty to protect all of its population.**

[104] Bouchard, Toxicological review of the regulatory framework for the nickel industry for the ambient air component, 2018, 104 pages.

Portrait of populations affected by nickel pollution

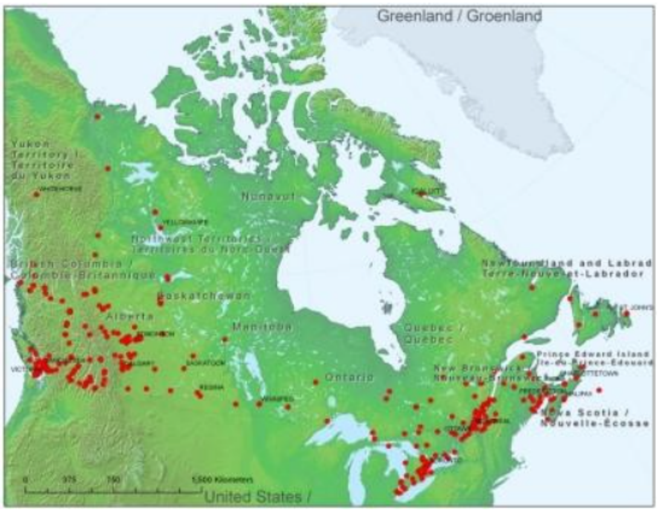
Inuit population near the Raglan mine

On the map of air pollutant sensors at the MELCC and Environment Canada sites, there are no air pollutant sensors in the vicinity of the Raglan mine (Figures 1, 2 and 3).

Figure 1: Map of MELCC air pollutant sensors

[105]

Figure 2: Map of Environment Canada's air pollutant sensors



[106]

[105] https://www.environnement.gouv.qc.ca/air/reseau-surveillance/Carte.asp

[106] https://www.canada.ca/fr/environnement-changement-climatique/services/pollution-atmospherique/reseau-surveillance-donnees/programme-national-pollution-atmospherique/emplacement-stations.html

In correspondence between the MELCC and Glencore Canada Corporation dated July 11, 2017 and subject *Raglan Mining Project -Phase II and III Project, Continuation of Mining Operations East of Katinniq*,[107] it is stated:

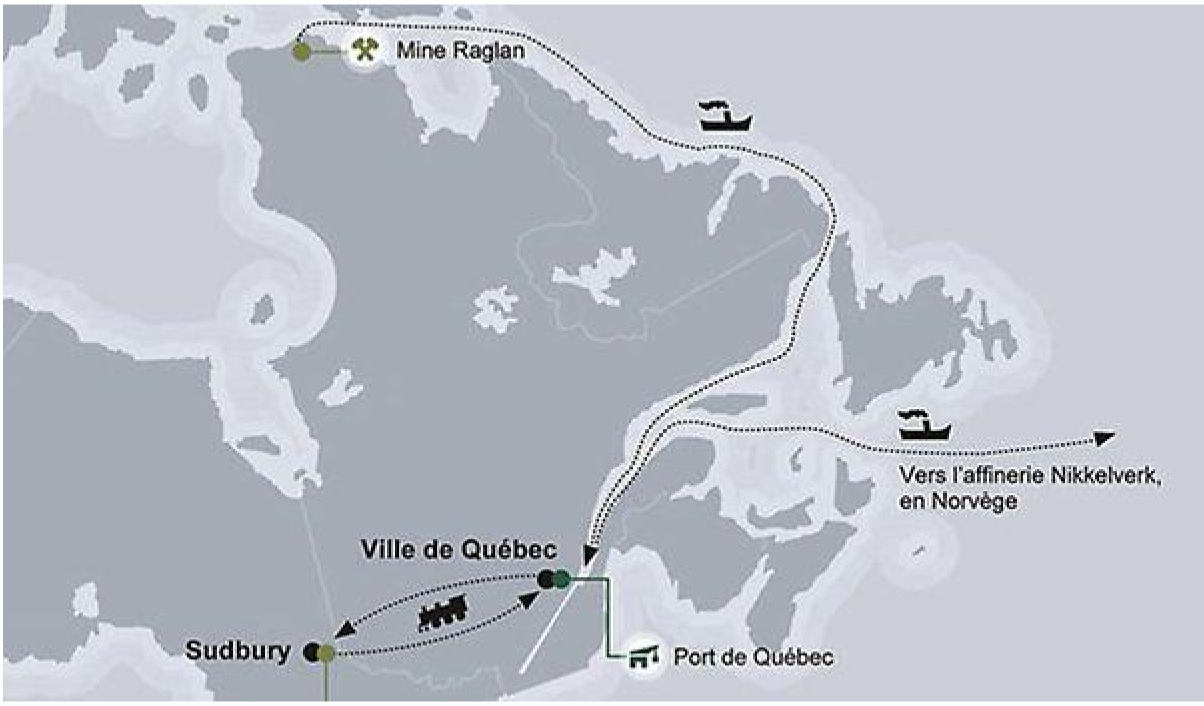
> *The proponent shall file with the Administrator, for information purposes, one year after the issuance of this amendment to the Certificate of Approval, an Air Emissions Management Plan including a description of the emission sources of the project and the mitigation measures it has committed to implement as part of the project. It will include the dust management plan for the area of the road near Deception Bay and will specify if the mitigation measures need to be adjusted.*

However, we were unable to find this management plan on the MELCC website. It was therefore impossible for us to evaluate the PM and nickel concentration levels to which the population surrounding the Raglan Mine is exposed. As a result of this failure, and due to the tight schedule, we stopped our research on the pollution levels to which other populations in the vicinity of other mining sites are exposed.

Population of Quebec City

A map found on the Glencore website clearly shows that Quebec City, with its Port of Quebec, is a hub on the nickel route in Quebec (Figure 3).

Figure 3: Map of the Raglan Mine nickel route



108

[107] https://www.environnement.gouv.qc.ca/evaluations/projet/maj/2017/3215-14-019.pdf
[108] https://www.glencore.ca/fr/raglan/who-we-are/at-a-glance

Concentrations of nickel and other pollutants

The CLSC Basse-Ville-Limoilou-Vanier territory has a history of air pollution with high levels of nickel (Table 4).

Table 4. Average nickel and total particulate matter (TPM) concentrations for the period 2 April 2010 to 28 March 2012 from a *Hi-Vol* sampler

	Nickel	PST	% de nickel dans PST
Station Des Sables	0,07236 µg/m³ (72 ng/m³) (n=80)	45,5 µg/m³ (n=80)	0,159
Station Vitré	0,04875 µg/m³ (49 ng/m³) (n=112)	61,3 µg/m³ (n=112)	0,080
Station Beaujeu	0,03883 µg/m³ (39 ng/m³) (n=102)	56,0 µg/m³ (n=102)	0,069

Adapté de J.-F. Brière (2012) Incinérateur de Québec : Analyse des résultats de métaux. Direction du suivi de l'état de l'environnement, ministère du Développement durable, de l'Environnement et des Parcs, 7 décembre 2012

[109]

On the MELCC site, only one sensor is currently reported to be in operation for metals on the territory of Quebec City. This is the one in Vieux-Limoilou (Figure 4).

Figure 4: Characteristics of the Québec-Vieux-Limoilou pollutant collection station

Québec - Vieux-Limoilou

No. station : 03006
Municipalité : Québec
Ouverture : 1989-08-14

Contaminants mesurés de façon continue :
PM2,5, O3, NOx, SO2, CO

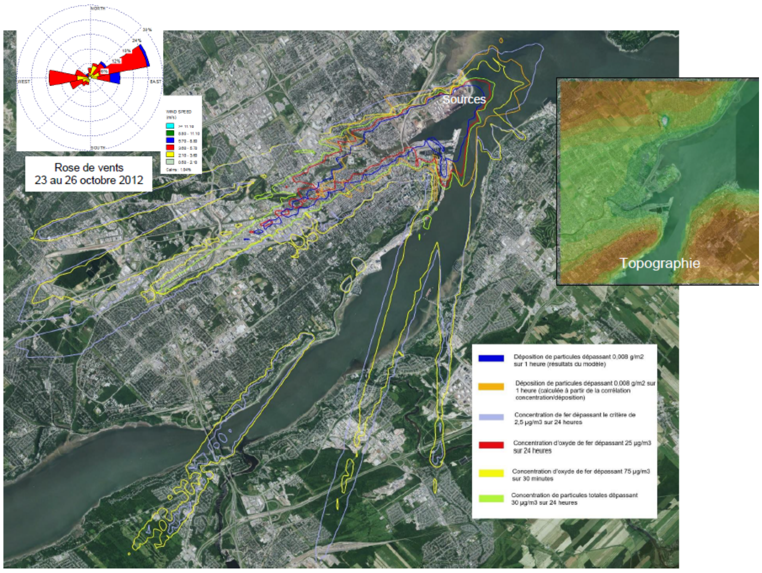
Contaminants mesurés de façon séquentielle :
PST, PM10, Métaux, COV [110]

It is therefore difficult to know what levels of nickel are exposed to in other parts of Quebec City. If we assume that the transshipment and/or storage of nickel concentrate in the Beauport sector of the Port of Québec is the source of nickel pollution in Limoilou,[111] a dispersion study conducted on iron ore emissions from the same source suggests that the population impacted by nickel pollution could be greater than the population of the neighbourhoods surrounding the Port of Québec (Figure 5).[112]

[109] Goupil-Sormany, Levque and Sebez. ATMOSPHERIC CONTAMINATION IN THE LA CITÉ-LIMOILOU DISTRICT: The Nickel Issue. Direction régionale de santé publique de l'Agence de la santé et des services sociaux de la Capitale-Nationale, 2013, 26 pages.
[110] https://www.environnement.gouv.qc.ca/air/reseau-surveillance/Carte.asp
[111] Walsh and Brière, Origine des concentrations élevées de nickel dans l'air ambiant à Limoilou, MELCC, 2013, 21 pages.
[112] Dionne, Estimation des taux d'émission de particules et étude de la dispersion atmosphérique pour déterminer le territoire affecté par les activités d'Arrimage du St-Laurent au port de Québec concernant la déposition de poussière perçue le 26 octobre 2012, Dans le cadre du recours collectif Lalande et Duchesne c. Compagnie d'arrimage de Québec et Administration portuaire de Québec, No 200-06-000157-134. Report #026-031, February 12, 2016, 144 pages.

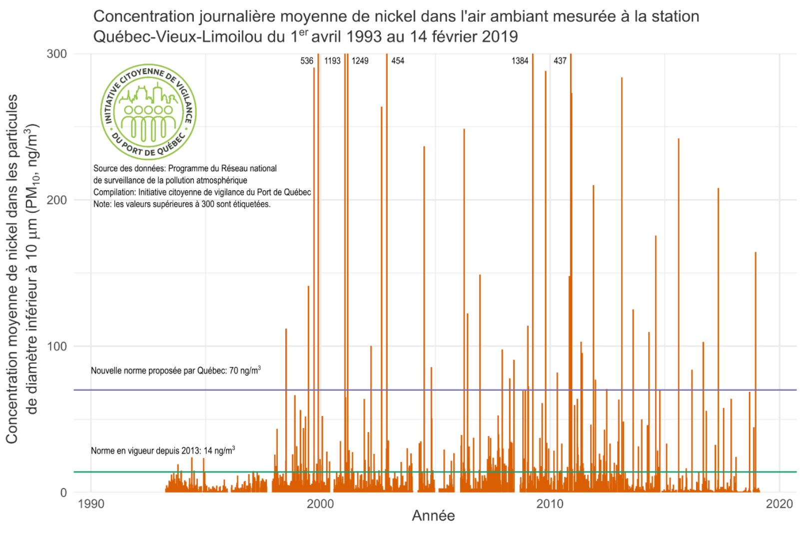
In fact, this dispersion study shows that iron ore particles from the Port of Québec could reach Place Duplessis on the north shore and sectors of Lévis on the south shore.

Figure 5. Atmospheric dispersion study to determine the area affected by iron ore handling activities at the Port of Quebec



The daily average concentration of nickel in PM $_{10}$varies greatly with daily peaks that can exceed 1000 ng/m^3 nickel in PM $_{10}$(Figure 6).[113]

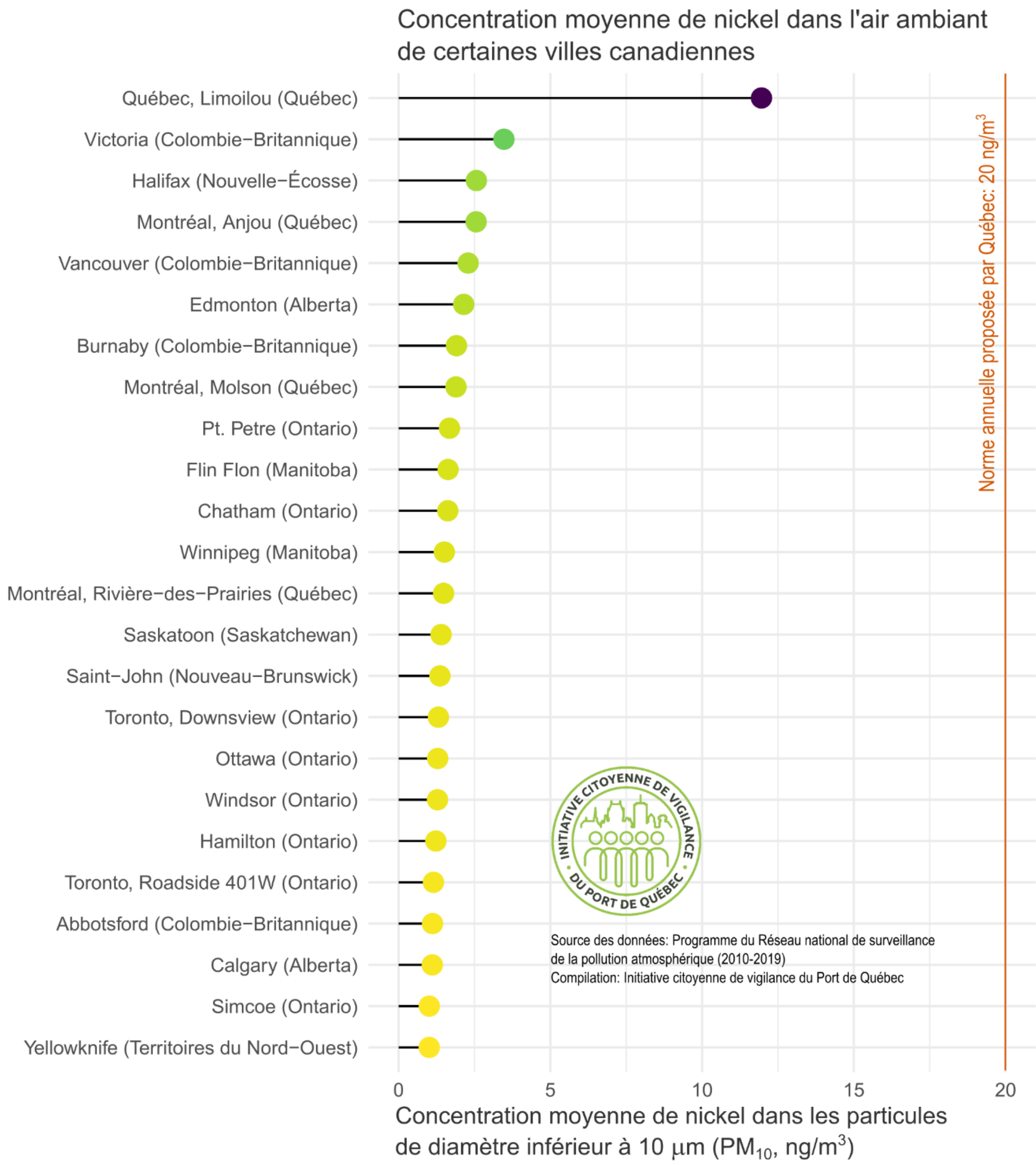
Figure 6. Average daily ambient air concentration measured at the Québec City-Vieux-Limoilou station from April 1, 1993 to February 14, 2019



[113] National Air Pollution Surveillance Network Program (2010-2019). Data compiled by the Citizen's Vigilance Initiative for the Port of Quebec, 2022.

If we compare the average concentration of nickel in PM_{10} in Québec-Limoilou, we see that it is much higher than in other major Québec or Canadian cities (Figure 7).[114]

Figure 7. Average ambient air concentrations of nickel in Canadian cities from 2010 to 2019



According to the Canadian Impact Assessment Agency's report published in 2020, the population of the area surrounding the Port of Québec is already subject to an environment saturated with air pollutants, with concentrations exceeding certain AAR and NAAQS standards (initial concentrations in Table 5).[115]

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[114] National Air Pollution Surveillance Network Program (2010-2019). Data compiled by the Citizen's Vigilance Initiative for the Port of Quebec, 2022.
[115] https://www.iaac-aeic.gc.ca/050/documents/p80107/136694F.pdf

Table 5. Summary of maximum concentrations of certain contaminants in ambient air during construction of the terminal in year 2

Contaminant	Période	Contribution maximale du projet (A)[1]		Concentration initiale (B)		Concentration totale (C = A + B)[2]		Norme ou critère	
		µg/m³	% norme	µg/m³	% norme	µg/m³	% norme	µg/m³	Type
Composés organiques volatils (COV)									
Formaldéhyde	*15 minutes*	*85*	*228 %*	*3*	*8,1 %*	*88*	*237 %*	*37*	*RAA*[3]
1,3-butadiène	*Annuelle*	*0,00041*	*0,14 %*	*0,27*	*90 %*	*0,3*	*90 %*	*0,3*	*NCQAA*[4]
Métaux									
Arsenic	*Annuelle*	*6,4 x 10⁻⁶*	*0,21 %*	*0,0027*	*90 %*	*0,0027*	*90 %*	*0,003*	*RAA*
Nickel (PM10)	*24 heures*	*0,0054*	*39 %*	*0,079*	*564 %*	*0,0844*	*603 %*	*0,014*	*RAA*
Matières particulaires[5] et dioxyde d'azote									
	24 heures	*27*	*90 %*	*20*	*67 %*	*47*	*157 %*	*30*	*RAA*
$PM_{2.5}$ (80 % atténuation)		*7,7*	*28 %*	*25*	*93 %*	*33*	*121 %*	*27*	*$NCQAA_{(2020)}$*
	Annuel	*0,56*	*6,3 %*	*9,7*	*110 %*	*10*	*117 %*	*8,8*	*$NCQAA_{(2020)}$*
PM_{10} (80 % atténuation)	*24 heures*	*19*	*31 %*	*48*	*80 %*	*67*	*111 %*	*60*	*60*[6]
PMT (80 % atténuation)	*24 heures*	*184*	*153 %*	*104*	*87 %*	*288*	*240 %*	*120*	*RAA*
Dioxyde d'azote (NO_2)	*1 heure*	*523*	*126 %*	*107*	*26 %*	*630*	*152 %*	*414*	*RAA*
	1 heure	*204*	*258 %*	*98*	*104 %*	*230*	*291 %*	*79*	*$NCQAA_{(2025)}$*
	24 heures	*227*	*110 %*	*75*	*36 %*	*302*	*146 %*	*207*	*RAA*
		9,7	*9,4 %*	*16*	*16 %*	*26*	*25 %*	*103*	*RAA*
	Annuelle	*9,0*	*39 %*	*16*	*70 %*	*25*	*109 %*	*23*	*$NCQAA_{(2025)}$*

Source : Adapté de Englobe, 2020c

RAPPORT PROVISOIRE D'ÉVALUATION ENVIRONNEMENTALE – PROJET LAURENTIA : QUAI EN EAU PROFONDE DANS LE PORT DE QUÉBEC – SECTEUR BEAUPORT 59

[116]

Comparing ambient concentrations with the new Health Organisation guidelines published in 2021, we find even greater and more widespread exceedances of pollutant concentrations for all the pollutants included in the new WHO guidelines and reported by the AIEC, including PM, the category of pollutants to which atmospheric nickel belongs (Table 6).

Table 6. Comparisons of pollutant levels reported by the AIEC in 2020 for the area surrounding the Port of Québec with the new WHO guidelines issued in 2021

Pollutant (µg/m³)	Time	WHO 2021 guidelines (µg/m³)	Levels reported by AIEC (µg/m³)
PM2.5	Annual	5	9.7
	24-Hours	15	25
PM10	Annual	15	N/A
	24-Hours	45	48
NO2	Annual	10	16
	24-Hours	25	75

[116] Ibid.

Origin and composition of nickel

In the MELCC[117] report *Origine des concentrations élevées de nickel dans l'air ambiant à Limoilou (Origin of the high concentrations of nickel in the ambient air in Limoilou)* submitted in 2013, it is stated:

> Elevated concentrations of nickel were measured in the ambient air at three MDDEFP stations in the Limoilou district of Quebec City. Two of these stations, Beaujeu and De Vitré, were in operation from April 2010 to March 2012, as part of a special project to assess the effects of the Québec City incinerator on air quality in the Limoilou neighbourhood. The third station, Des Sables, is a permanent station in the Quebec network that was also used specifically for this project to conduct metal analyses.
>
> The average annual nickel concentrations at these three stations range from 0.012 to 0.096 µg/m^3. They are higher than the usual urban concentrations, which are estimated to be between 0.001 and 0.004 µg/m^3, and higher than the annual standard of 0.012 µg/m^3 of nickel in ambient air adopted by Quebec in 2011 in the Regulation respecting the purification of the atmosphere. These results indicate the presence of one or more significant emission sources in the environment of the stations.
>
> At the Port of Quebec, Beauport sector, St. Lawrence Stevedoring transships large tonnages of pentlandite concentrate, the iron nickel sulfide ore used in nickel production. Pentlandite is extracted and concentrated in two mines, Raglan (Xstrata) in northern Quebec and Voisey's Bay (Vale Inco) in Labrador. The concentrate is shipped to Quebec City in dedicated ships: the MV Arctic (Raglan) and the Umiak 1 (Voisey's Bay). It is unloaded and stored at the Port of Quebec from where it is finally shipped by train to Sudbury where nickel matte is produced, i.e. a nickel metal that is not yet fully refined (the final refining is done in Europe). These transshipment activities are all responsible for the high concentrations of nickel in the air in the Limoilou district.
>
> In order to ascertain this, the MDDEFP sampling results were studied, and it turns out that, from three angles of analysis, the data indicate that nickel in suspended particles does indeed originate from the Port of Québec sector: 1) the relationship between nickel concentrations and wind direction, 2) the relationship between cobalt and nickel, and 3) the mineralogical analysis of dust and suspended particles.
>
> *1) Relationship between nickel concentrations and wind direction*
> The results of the nickel concentrations were studied as a function of wind direction at the De Vitré and Des Sables stations and as a function of the location of two potential emission sources, the port and the Québec City incinerator. A statistically significant relationship was found between the nickel concentrations observed at the De Vitré and Des Sables stations and the number of hours of wind from the port. Thus, during a sampling day, the greater the frequency of winds from the port, the higher the nickel concentrations at the stations. There is no relationship between the winds from the incinerator and the nickel concentrations at the sampling stations.
>
> *2) Correlation between cobalt and nickel*
> A close association between nickel and cobalt concentrations was observed, indicating that the source of both metals should be the same. Cobalt is present in the ore mined at the Voisey's Bay mine. The average ratio of nickel to cobalt concentrations in the suspended particulate samples is approximately 25, similar to that observed in a concentrate sample from Umiak 1 collected by the CCEQ de la Capitale-Nationale.

[117] Walsh and Brière, Origine des concentrations élevées de nickel dans l'air ambiant à Limoilou, MELCC, 2013, 21 pages.

3) Mineralogical analysis of dust and suspended particles

Dustfall samples collected by the MDDEFP in Limoilou and air sampling filters from the Des Sables station were analysed in the laboratory of Professor Josée Duchesne of the Department of Geology and Geological Engineering at Laval University. Scanning electron microscopy (SEM) analysis revealed that the nickel in the dust and suspended particulate samples was mainly in the form of pentlandite. Pentlandite is a sulfide of iron and nickel with the chemical formula $(Fe,Ni)_9S_8$. Pentlandite is often associated with pyrrhotite and may also contain cobalt. Pentlandite is not found naturally in dust in a city like Quebec. In conclusion, it appears very unlikely that the high concentrations of nickel measured in the air in Limoilou could come from any source other than the transshipment and/or storage of nickel concentrate in the Beauport sector of the Port of Québec.

In the same report, it is stated that in the suspended particulate filter from air sampling at the Des Sables station, which contained a high concentration of nickel (133ng/m^3), the **bulk of the nickel was in the form of pentlandite.**

Existing vulnerabilities of the population of Quebec City affected by air pollution

Socio-economic vulnerabilities

The socio-economic disadvantage of the population affected by high nickel levels is well known. Thus, we can read in the opinion of the Direction de santé publique du CIUSSS de la Capitale-Nationale issued in 2021:[118]

> Socio-health data published in 2012 show that the population of the CLSC Basse-Ville/Limoilou-Vanier territory generally presents a less favourable picture for several health determinants and conditions than the rest of Quebec. For example, the proportions of people living below the low-income cut-off, single-parent families with children under 18 years of age, smokers in the 12-and-over age group, and low-weight births are higher. The mortality rate for malignant tumours, respiratory and circulatory diseases is also higher. Life expectancy in good health is lower than elsewhere in Quebec (DSP Capitale-Nationale 2015). The greatest regional concentration of disadvantage, both material and social, is found in the CLSC Basse-Ville/Limoilou-Vanier territories (DSP Capitale-Nationale, 2012).

Environmental and climatic vulnerabilities

In addition to being exposed to levels of pollutants exceeding RAA and NAAQS standards and WHO guidelines, the population affected by airborne nickel pollution is also environmentally and climatically disadvantaged.

As mentioned above, urban trees can capture significant amounts of air pollutants. Other health, social and environmental benefits of urban trees have been reported to include reduced risk of cardiovascular disease, asthma, obesity, hypertension, diabetes, stress, depression, autism, cancer,

[118] Révision de la norme de qualité de l'atmosphère sur le nickel du Règlement sur l'assainissement de l'atmosphère, Position de la Direction de santé publique du Centre intégré universitaire de santé et de services sociaux de la Capitale-National, 2021, 6 pages.

premature mortality, [119] symptoms of attention deficit hyperactivity disorder,[120] a slowing of cognitive decline,[121] a decrease in social[122] isolation and crime,[123] an increase in school[124] performance and work productivity,[125] a reduction in car speed,[126] rainwater management,[127] the fight against social disadvantage,[128] heat islands [129]and climate change (CO_2 capture).[130]

However, the canopy index of the area affected by nickel pollution, which varies between 13 and 18%,[131] is well below the level considered optimal, which is at least 40% in naturally forested regions such as ours.[132]

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[119] Greening Cities for Population Health, Beaudoin and Levasseur, INSPQ 2017, 103 pages. Reference cited: Townsend, Ilvento and Barton, 2016.
Health Benefits from Nature Experiences Depend on Dose, Danielle F. Shanahan, Robert Bush, Kevin J. Gaston, Brenda B. Lin, Julie Dean, Elizabeth Barber & Richard A. Fuller, Scientific Reports 6, Article number: 28551 (2016)
Inverse relationship between urban green space and childhood autism in California elementary school districts, Jianyong Wua, Laura Jackson, Environment International 107 (2017) 140-146
Neighborhood Greenness and Chronic Health Conditions in Medicare Beneficiaries, Scott C. Brown, PhD,1,2 Joanna Lombard et al. Am J Prev Med 2016;51(1):78-89.
Urban Green Spaces and Health, Stephen Vida, National Institute of Public Health, 2011. Reference cited: Ellaway et al, 2005
Assessing the Potential of Land Use Modification to Mitigate Ambient NO_2 and Its Consequences for Respiratory Health. Rao M., George LA et al. Int J Environ Res Public Health. 2017 Jul 10;14(7). pii: E750. doi: 10.3390/ijerph14070750.
Urban greenness and mortality in Canada's largest cities: a national cohort study, Dan Crouse, Lauren Pinault, et al, The Lancet Planetary Health, Volume 1, Issue 7, October 2017, Pages e289-e297
Exposure to greenness and mortality in a nationwide prospective cohort study of women. James P, Hart JE, Banay RF, Laden F. 2016. Environ Health Perspect 124:1344-1352.

[120] Association between exposure to the natural environment, rurality, and attention-deficit hyperactivity disorder in children in New Zealand: a linkage study. Geoffrey HDonovan, Yvonne LMichael, Demetrios Gatziolis, The Lancet Planetary Health Volume 3, Issue 5, May 2019, Pages e226-e234

[121] Residential Surrounding Greenness and Cognitive Decline: A 10-Year Follow-up of the Whitehall II Cohort. de Keijzer C1,2,3, Tonne C1,2,3, Basagaña X1,2,3, Valentín A1,2,3, Singh-Manoux A4,5, Alonso J2,3,6, Antó JM1,2,3, Nieuwenhuijsen MJ1,2,3, Sunyer J1,2,3, Dadvand P1,2,3. Environ Health Perspect. 2018 Jul 12;126(7):077003. doi: 10.1289/EHP2875.

[122] How innovative city planning can aid healthy aging in place Evaluating the success of the Comox-Helmcken Greenway under the aspect of age-friendly community planning, Stephan Zimmermann B.Sc., Research Project Submitted in Partial Fulfillment of the Requirements for the Degree of Master of Resource Management, Simon Fraser university, 2016, 72 pages. http://summit.sfu.ca/item/16123

[123] Economic values of metro nature health benefits: A life course approach, Kathleen L. Wolf a,⁎ , Marcus K. Measells b, Stephen C. Grado b, Alicia S.T. Robbins, Urban Forestry & Urban Greening 14 (2015) 694-70.

[124] Sivarajah S. et al, Tree cover and species composition effects on academic performance of primary school students. PLoS One. 2018 Feb 23;13(2):e0193254. doi: 10.1371/journal.pone.0193254.

[125] Heschong, L., Heschong Mahone Group (2003) Windows and Offices: A Study of Office Worker Performance and the Indoor Environment. California Energy Commission: Pacific Gas and Electric Company. Fair Oaks, California.

[126] The Street Tree Effect and Driver Safety, Naderi, Kweon et al, ITE Journal on the web / February 200869-73.

[127] ÉTUDE DES BIOTOPES URBAINS ET PÉRIURBAINS DE LA CMM, Labrecque and Vergriete, Conseil régional de l'environnement de Laval, 2006, 23 p.

[128] Health Disparities in the Relationship of Neighborhood Greenness to Mental Health Outcomes in 249,405 U.S. Medicare Beneficiaries. Brown SC1,2, Perrino T3, Lombard J4,5, Wang K6,7, Toro M8, Rundek T9,10, Gutierrez CM11, Dong C12, Plater-Zyberk E13, Nardi MI14, Kardys J15, Szapocznik J16,17. Int J Environ Res Public Health. 2018 Mar 1;15(3). pii: E430. doi: 10.3390/ijerph15030430.

[129] Lafontaine-Messier, Mariève, Alain Olivier and Bruno Chicoine. 2010. "The Potential Contribution of the Urban Forest to the Sustainable Development of Quebec Cities. Les Cahiers de l'Institut EDS, Série Stratégies du développement durable, numéro 1 (February), p.1-30.

[130] Sustaining & Expanding the Urban Forest: Toronto's Strategic Forest Management Plan. Toronto, Ontario. City of Toronto, Parks, Forestry and Recreation, Urban Forestry, 2013.

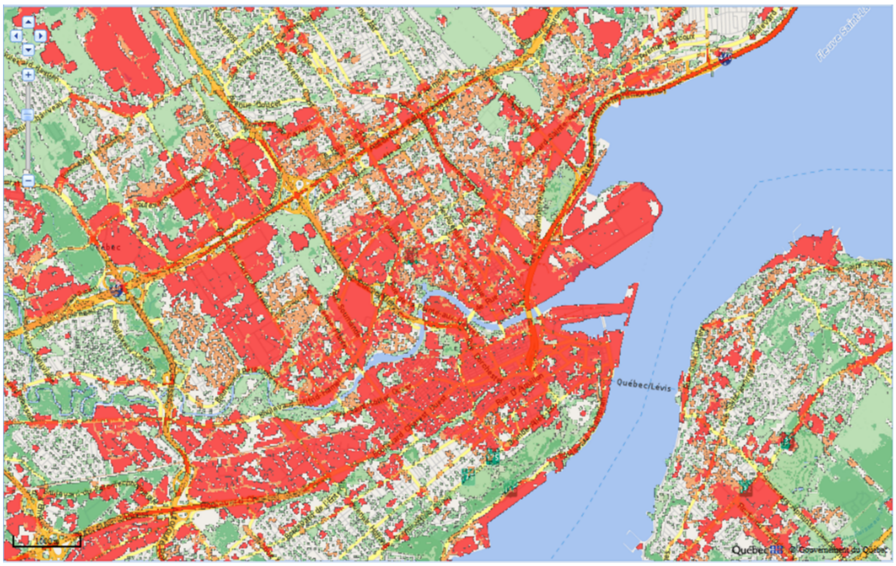
[131] https://www.ville.quebec.qc.ca/apropos/planification-orientations/environnement/milieuxnaturels/docs/bilan_vision_arbre_2015_2020.pdf

[132] USDA Forest Service (2016). The Sustainable Urban Forest. A Step-by-Step Approach. Retrieved from http://www.itreetools.org/resources/content/Sustainable_Urban_Forest_Guide_14Nov2016.pdf

The presence of trees, urban woodlands and other natural elements increases the attractiveness of routes and encourages active transport.[133] Trees make routes more comfortable for pedestrians and public transport users as they provide protection from the sun in summer and wind in winter.[134] The presence of biodiversity is also an attractive element for humans, encouraging them to walk to public transport or other places while calming and refreshing them mentally.[135]

Urban heat islands are known to have a negative impact on the health of the population. Areas affected by nickel pollution are home to huge heat islands that are harmful to health (Figure 8).

Figure 8. Map of heat islands in Quebec City



Potential impact of air pollution on the future of this sector

In addition to the scientific community, more and more citizens in this area are becoming aware of the health impacts of air pollution on their lives. If the situation persists, it could diminish the attractiveness of this sector, hinder its development and requalification and reduce the profitability of current and future municipal infrastructures. It is therefore the densification of this central sector of Quebec City that could be at stake, as well as its corollary, the fight against urban sprawl, if the air pollution problem persists.

Economic analysis

One of the principles of sustainable development is to internalise costs. However, the study entitled *Economic Impact Assessment of the Nickel Standard and Industry in Quebec is* incomplete because it does not take into account the economic value of the health impacts of air pollution generated by

[133] Built environmental correlates of cycling for transport across Europe. Mertens L1, Compernolle S1, Deforche B2, Health Place. 2017 Mar;44:35-42. doi: 10.1016/j.healthplace.2017.01.007.
[134] Effects of trees on mean wind, turbulence and momentum exchange within and above a real urban environment. M.G. Giometto, A. Christen, P.E. Egli, Advances in Water Resources, 2017; 106: 154 DOI: 10.1016/j.advwatres.2017.06.018
[135] Connecting global priorities: biodiversity and human health: a state of knowledge review. World Health Organization and Secretariat of the Convention on Biological Diversity, 2015, 365 p.

this industry in Quebec. This value may be significant since the total economic value of the health impacts of air pollution for Quebec is estimated at $30 billion per year. [136]

For example, in a brief submitted to the Canadian Impact Assessment Agency, we calculated the economic impact of the Laurentia project using a previous Health Canada study that estimated the health impact of air pollution at $28 billion per year.[137] The Port of Quebec estimated that 457 direct and 316 indirect jobs would be created and that the added value, both direct and indirect, would amount to $86.3 million annually during the operational phase. Based on the proportion of premature deaths in Quebec City (300/3,800 deaths) and the population of the boroughs of Cité-Limoilou (107,885 inhabitants) and Beauport (80,925 inhabitants) in relation to the population of Quebec City (531,902 inhabitants[138]), the value of the current air pollution costs in the boroughs of Cité-Limoilou and Beauport was estimated at approximately $785 million per year. An increase of 0.41 $\mu g/m^3$ from the initial value of 9.7 $\mu g/m^3$ of annual $PM_{2.5}$ (4.2% increase) would have been equivalent to approximately $33 million per year and an increase of 92 $\mu g/m^3$ from the initial value of 98 $\mu g/m^3$ of annual NO_2 (94% increase) would have been equivalent to $736 million per year. These calculations demonstrate the potential economic impact of small increases in air pollutants.

We believe it is important to assess the economic value of the health impacts of air pollution from the nickel industry and to integrate them into the economic analysis in order to establish a more accurate picture of the situation for Quebec taxpayers. This is all the more important as we are experiencing a probable explosion in health costs, linked in particular to the sedentary nature of the population, to technological and pharmacological advances that are often expensive, to the ageing of the population and to climate change, in a current context of congestion in the health system and problems of access to health care.

According to our research, the nickel industry appears to be a thriving industry with the world nickel price jumping from US$4/lb in 2017 to almost US$10/lb in 2021 (Figure 9). Furthermore, despite the adoption of the 14 ng/m^3 24-hour RAA standard for nickel in 2013, Glencore, one of the prominent companies in the Quebec nickel industry, has seen the split-adjusted closing price and dividend payments of Glencore's stock rise from £210.87 on 1 January 2014 to £395.35 on 1 January 2022.[139] The same company approved capital to develop the Raglan Mine Sivumut project in Nunavik in 2017. The RAA standard adopted in 2013 does not appear to have hindered or driven away this company's expansion, quite the contrary, judging by the Raglan Mine expansion project decided in 2017.

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[136] Health Impacts of Air Pollution in Canada, Estimated Morbidity and Premature Deaths, Report 2021, Health Canada, Publ: 200424, 62 pages.
[137] Brief submitted to the Canadian Impact Assessment Agency as part of the public consultation on the Laurentia Project, AQME, 2020, 25 pages.
[138] https://www.ville.quebec.qc.ca/apropos/portrait/quelques_chiffres/ville/index.aspx
[139] https://finance.yahoo.com/quote/GLEN.L/history?period1=1388534400&period2=1641513600&interval=1mo&filter=history&frequency=1mo&includeAdjustedClose=true

Figure 9. Nickel price trends since 2017

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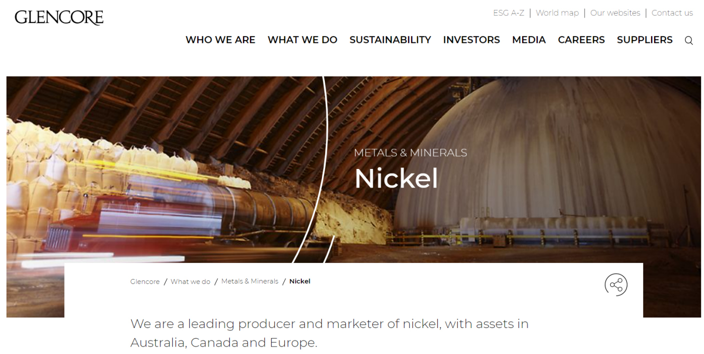
Covering nickel handling and transhipment operations is proposed as one of the technical means to limit atmospheric nickel emissions.[141] In view of the rising world price of nickel, it seems reasonable to us to ask this industry to cover its operations rather than raise the nickel standard to the detriment of public health and public finances. Glencore's webpage dedicated to its nickel operations shows covered facilities (Figure 10). [142]

Figure 10. Screenshot from Glencore's website



143

[140] http://www.kitcometals.com/charts/nickel_historical_large.html
[141] https://uploads.visionw3.com/sitefiles/canadianroyalties.com/documents/2019/mitigation_measures_french.pdf
[142] https://www.glencore.com/what-we-do/metals-and-minerals/nickel
[143] https://www.glencore.com/what-we-do/metals-and-minerals/nickel

Recommendations

Because of nickel's carcinogenic effects, its potential adverse effects on the respiratory, cardiovascular, immune and nervous systems, its disproportionate impact on children, and its association with increased non-accidental mortality demonstrated in Canadian cities, we consider this to be an important health issue.

With this in mind, we make the following recommendations:

Protecting human health from nickel air pollution

Whereas

- According to the Quebec Charter of Rights and Freedoms, every person has the right, to the extent and according to the standards provided by law, to live in a healthy environment that respects biodiversity.[144]
- There are no airborne nickel sensors near all populations that may be exposed to nickel pollution, including the Inuit population residing near the Raglan mine.
- The Quebec population known to be impacted by nickel pollution, i.e. those residing in the CLSC Basse-Ville-Limoilou-Vanier area, is disadvantaged from a socio-economic, environmental and climatic point of view.
- The population's awareness of the negative impacts of air pollution on health and life could hinder the densification, requalification and development of the CLSC basse-Ville-Limoilou-Vanier territory.
- The extent and severity of nickel air pollution is poorly documented due to a lack of air pollutant sensors, while the geographical distribution of nickel pollution is probably underestimated based on a dispersion study done for another ore in the Quebec City area.
- The economic analysis of the nickel industry is incomplete as it does not take into account the value of the health impacts of nickel air pollution.
- The RAA standard of 14 ng/m^3 24-hours of nickel in PM_{10} adopted in 2013 does not seem to have scared off mining companies, on the contrary, if the Raglan Mine expansion project decided in 2017 by Glencore is any indication.
- A study by the MELCC concluded that it is highly unlikely that the high concentrations of nickel measured in the air in Limoilou could come from any source other than the transshipment and/or storage of nickel concentrate in the Beauport sector of the Port of Québec.
- Simple and feasible technological solutions exist while the nickel industry seems to be flourishing if the price of nickel is anything to go by.
- Recent scientific and epidemiological evidence on the health impacts of fine particulate matter (PM), the category of air pollutant to which nickel belongs, has led the World Health Organisation to lower its guidelines for $PM_{2.5}$ and PM_{10}
- Studies in rats and mice for non-cancer effects of nickel are inappropriate in view of the new potential effects reported in the scientific literature, particularly on the cardiovascular and central nervous systems, the lack of sensitivity of the rodent lines used to human pathologies such as atherosclerosis and Alzheimer's disease, and the development of more effective diagnostic tools that have emerged over the last 20 years.

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[144] http://www.legisquebec.gouv.qc.ca/fr/document/lc/C-12

- Studies in rats and mice for non-cancer effects are deficient in that they were done in young adults of these species, whereas nickel is a toxic air contaminant that has a disproportionate impact on children.
- The European standard, the California RELS and the Ontario standard were based on the non-cancer effects of nickel sulphate (the less carcinogenic form). The adopted standards based on the non-cancer effects of nickel sulphate were considered protective against the cancer effects of nickel because speciation studies in Europe and Ontario showed that nickel sulphate was the predominant airborne form while subsulfide (the more carcinogenic form) accounted for only 10-30% of nickel pollution. The situation in Quebec is different. Indeed, the speciation study carried out in 2013 by the MELCC on the territory of Quebec City shows that most of the atmospheric nickel is in the form of nickel-iron sulfide (**pentlandite**), a compound for which an increase in lung cancer mortality has been reported in pentlandite miners. The Quebec standard should therefore be based on the cancerous effects of nickel at a negligible risk level of one additional case per million people exposed over a lifetime.

Recommendations

We recommend that the Government of Quebec:

- Adopt an annual standard based on the World Health Organisation's unit risk for cancer to be consistent with the negligible risk level for the occurrence of the MELCC effect set at one additional case of cancer per million people exposed over a lifetime: **3 ng/m^3 annual nickel in PM$_{10}$.**
- Retain the 24-hour standard before revision of **14 ng/m ^{3}24-hour nickel in PM$_{10}$.**
- Install atmospheric nickel sensors in the vicinity of all populations in Quebec likely to be exposed to nickel air pollution and publish the data.
- Conduct research into the potential harmful effects of pentlandite, using human epidemiological studies and appropriate animal models.
- Further investigate the potential synergistic effects of nickel with other air pollutants as recommended in the new federal Strengthening Environmental Protection for a Healthier Canada Act to modernize the Canadian Environmental Protection Act, 1999 (CEPA).
- Promote the implementation of practices that could reduce pollutant emissions associated with industrial activities.

Protecting human health from air pollution in general

Whereas

- Air pollution is associated with 4000 premature deaths per year in Quebec.
- The economic value of health impacts has been estimated at $30 billion per year in Quebec.
- As a result of accumulating scientific evidence of the harmful effects of air pollutants at very low concentrations, the World Health Organization has lowered its guidelines for several key pollutants in 2021.

Recommendations

We recommend that the Government of Quebec:

- Adopt these standards recommended by the World Health Organization in 2021:

Pollutant (µg/m^3)	Time	WHO 2021 guidelines (µg/m^3)
PM2.5	Annual	5
	24-Hours	15
PM10	Annual	15
	24-Hours	45
NO2	Annual	10
	24-Hours	25
O3	During the high season	60
	8-hours	100
SO2	24-Hours	40
CO	24-Hours	4

- Display in real time the levels of air pollutants measured in the main cities of Quebec, based on Airparif. [145]
- Adopt a regulation governing an emergency mechanism in the event of air pollution peaks, as in Geneva. [146]
- Investing in public and active transport to reduce air pollutant emissions.
- Ban the advertising of gas-guzzling motor vehicles, including sport utility vehicles (SUVs).
- Create a greening fund for cities to increase the capture of air pollutants by urban trees.
- Invest in an air pollution education campaign as part of an integrated plan to reduce the prevalence of disease and premature death from air pollution, ease congestion in the health system and reduce health costs.

Integrating health impacts cost-analysis

Whereas

- Some economic development projects can have major health impacts on the population.
- These health impacts can result in direct and indirect health costs that are substantial.

[145] https://airparif.asso.fr/
[146] https://silgeneve.ch/legis/data/rsg_K1_70p09.htm

- One of the principles of sustainable development is to internalize costs.
- Quebec's health care system has a chronic problem of congestion and access to health care.

Recommendations

We recommend that the Government of Quebec:

- Systematically conduct a health[147] impact assessment for any development project or standard that may have a significant effect on the health of the population.
- Systematically assess and integrate health costs into any economic analysis of a significant development project or standard that may have a significant impact on the health of the population.
- Create a Quebec Health Impact Agency with a mandate to assess the health impacts and costs associated with any significant development project or standard that may have a significant effect on the health of the population.

147 http://collectivitesviables.org/articles/l-evaluation-d-impact-sur-la-sante-eis.aspx#:~:text=It%20consists%20of%20a%20appr%C3%A9ciation,a%20%C3%A9team%20of%20multidisciplinary%20experts.

Conclusion

We hope that the recommendations in this brief will be retained in the revision of the nickel standard in order to better protect the health and well-being of the population, reduce health costs and fight against social and climate inequalities. We hope that the Quebec government will have the courage to ensure a healthy environment for its entire population in order to protect the lives of its citizens, reduce congestion in our health care system and, in so doing, better control public health care spending.

We remain available to discuss this further with you and to answer any questions you may have after reading this brief.

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