Evaluation of Competence of Route-to-route Extrapolation for Air Quality Guidelines: Comparison of Extrapolated Values from Oral Toxicity and Guideline Values of Toxic Metal Dusts

Master's Capstone Project

In Partial Fulfillment of the Requirement for the Degree of

Master of Public Health

Submitted by

Seon Yeoung Oh

The Faculty of Health Science

Simon Fraser University

June 2017

Senior Supervisor

Scott Venners

External Supervisor

Reza Afshari

Second Reader

Anne-Marie Nicol

Table of Contents

Abstract

Introduction:

Air pollution has become a major global environmental health concern, and the importance of adequate air quality guidelines has been highlighted. Crude measurements of total particulate matter (PM) are not sufficient to protect population health since some components of PM are more associated with certain adverse health effects. Toxic heavy metal dusts are commonly found in PM, and found to exceeded or approached guidelines. Current air quality guidelines are mostly based on route-to-route (RtR) extrapolation from oral exposure studies which is a conventional approach to substitute insufficient inhalation-specific exposure data.

Purpose:

This project aims to compare RtR limits extrapolated from oral exposure limits of metal dusts set by the regulatory bodies to their respiratory exposure limits and various air quality guidelines, to quantify the differences in values, and to evaluate the competence of the guidelines with application of oral-to-inhalation extrapolation.

Methods:

A systematic literature review on RtR extrapolation was performed along with a narrative review of documents from regulatory agencies in Canada and the US for assessing the current state of application of RtR extrapolation in air quality guidelines for environmental and occupational health purposes. Data was described and synthesized by calculating extrapolated values and comparing quantitatively.

Results and discussion:

The reliability of RtR extrapolation significantly depends on availability of toxicokinetic data. More route-specific studies are necessary to enhance the database. Extrapolated exposure limits are higher by 1 to 3 orders of magnitude than inhalation-specific minimal risk levels (MRL), possibly due to direct respiratory toxicity. This indicates reliance on RtR extrapolation alone to derive inhalation exposure limit is not sufficient to protect from adverse health effects. Environmental air quality guidelines are mostly below calculated RtR limits, but occupational air quality guidelines are generally above extrapolated exposure limits, posing concerns due to underestimation of toxicity.

Limitations of the study include insufficient toxicokinetic data on the possibility of direct toxicity and bioavailability, potential interaction between toxics under multiple-substance exposure scenarios, and lack of a federally managed Canadian database.

Public Health Implication and recommendations:

It is advised to measure and analyze particulate matter components in air, conduct more route-specific experiments and human epidemiology studies for various durations of exposure research, and use extrapolated RtR limits with case-specific RtR factors or an uncertainty factor of at least 10 for new standards. It is recommended to disseminate the knowledge to health authorities highlighting the caveat of using RtR alone. Reassessment of regulatory limits for occupational guidelines is recommended. Also, it is necessary to establish a domestic federal toxicological database.

Introduction

The World Health Organization (WHO) reports that air pollution has become a major environmental health concern, with nearly 4 million premature deaths attributable to ambient air pollution globally from causes such as cardiovascular diseases, cancers, and chronic and acute respiratory diseases caused by PM_{10} (particulate matter of 10 microns or less in diameter) in 2012 (World Health Organization, 2016a). More than 80% of urban inhabitants are exposed to air quality levels over WHO limits, and 98% of cities with population greater than 100,000 in low- and middle-income countries do not meet the WHO air quality guidelines[1] (World Health Organization, 2016b). In 2014, it was estimated that 92% of the global population was residing in places exceeding the WHO air quality guidelines levels, which are 10 $\mu g/m^3$ annual mean and 25 $\mu g/m^3$ 24-hour mean for $PM_{2.5}$ (particulate matter of 2.5 microns or less in diameter), and 20 $\mu g/m^3$ annual mean and 50 $\mu g/m^3$ 24-hour mean for PM_{10} (World Health Organization, 2016a). WHO acknowledges that even if the WHO air quality guidelines are intended to provide technical advice on policy formulation, each country may adopt different national standards based on the national context taking feasibility, capability, political factors, and socioeconomic considerations into account (World Health Organization, 2006). Therefore, adequate air quality guidelines and regulations for local contexts are crucial components of health policies to protect population health as well as occupational health.

Toxic metal dusts are commonly found in air, and guidelines entailing monitoring and analyzing metal dust components in air are important; the chemical composition of particulate matter

[1] "the term guideline refers to a prescribed ambient air concentrations that is not to be exceeded in the setting jurisdiction; guidelines can also be called objectives, standards, and criteria, and these terms are used inter-changeably herein" (Galarneau et al., 2016)

(PM) is closely related to toxicity, severity, and types of adverse health effects since certain components are more or less toxic than others (Lippmann & Chen, 2009). Accordingly, monitoring chemical components of PM will benefit implementation of targeted regulations on the most toxic components (Lippmann, 2010, 2012). It is alarming that toxic heavy metals such as nickel, arsenic, cadmium, and lead, measured in Canada by the National Air Pollution Surveillance from 2009 to 2013, exceeded or approached at least one provincial guideline, even when the actual concentration is acknowledged to be underestimated due to measurement methods; yet, no specific federal guidelines exist for ambient air toxics[2] in Canada (Galarneau et al., 2016). Adequate federal guidelines, including metal dusts control, based on scientifically rigorous evidences should be implemented for the best health outcome results.

Due to a lack of inhalation-specific exposure data, air quality guidelines are mostly developed based on oral exposure studies of toxic metals via route-to-route (RtR) extrapolation, which is one of conventional approaches to substitute unavailable route-specific information (Rennen, Bouwman, Wilschut, Bessems, & Heer, 2004). Problems arise with integrity of RtR extrapolation since toxicokinetic mechanisms of oral and inhalation routes vary, resulting in over- or underestimation of no-observed-adverse-effect-level (NOAEL) because of large uncertainty factors, especially for route-specific effects (Rennen et al., 2004). There are other factors that influence the validity and reliability of extrapolation, including study design, quality of oral studies used, and physicochemical properties of the chemicals (Schröder et al., 2016). Furthermore, the complexity of dose estimation via inhalation route obscures oral-to-inhalation extrapolation since respiratory dose calculation is a function of number of factors including

[2] Also known as hazardous air pollutants or air contaminants

concentration and duration of exposure, breathing patterns, absorption, and diffusion or deposition in lungs. Therefore, it is recommended not to use conventional default values from RtR extrapolation guidelines, but to calculate the conversion factor[3] for each specific setting to extrapolate oral to inhalation exposure (Pauluhn, 2003).

Purpose

The main purpose of this paper is knowledge translation and risk communication targeting environmental health professionals, to deliver knowledge of environmental and occupational regulations of metal dusts in air and, therefore, implement appropriate policies for environmental and occupational health.

This project aims to compare RtR inhalation exposure limits, extrapolated from oral exposure limits, to the research-based respiratory limits and various air quality guidelines, to quantify the differences in values, and ultimately to evaluate the competence of the guidelines with application of oral-to-inhalation extrapolation. The current promulgated guidelines are presumed inadequate as the exposure limits established by route-to-route extrapolation do not incorporate route-specific variability factors. The air quality guidelines of various heavy metals are reviewed to define the extent of accuracy of association between oral-to-inhalation extrapolated exposure limits and the guideline values. The oral-to-inhalation extrapolated exposure limits are compared to inhalation minimal risk limit (MRL), when available. The difference is quantified, and they are discussed with insight into the adequacy of the RtR extrapolation with recommendations proposed.

[3] To translate the limit of oral exposure to that of respiratory exposure based on the equipotent dose

Background Review of Air Quality Guidelines and Metal Components of Particulate Matter

In order to comprehend the current status of air quality guidelines and the competency to protect populations at risk, a background review was performed with academic and grey literature. For environmental air quality guidelines and occupational air quality guidelines, government databases were searched for existing guidelines. For risk assessments on metal dusts, "risk assessment metal dusts occupational health" and "risk assessment metal dust ambient air" were searched on PubMed. For health effects of vulnerable population, "air pollution health effects" was searched in combination with additional term, "pregnancy", "children", "elderly", or "pre-existing medical condition" to search the risks specific to respective populations. I searched titles and abstracts with the inclusion criteria: 1) articles in English and 2) articles in peer reviewed journals; after the screening based on the abstracts, irrelevant articles and articles unable to be located were excluded.

Current air quality guidelines

In Canada, only 6 provinces[4] where the majority of Canadian population reside, including British Columbia, promulgated ambient air guidelines for air toxics. Moreover, contaminants that are addressed and their guideline values are inconsistent across jurisdictions. For example, the objective concentration of nickel for 24-hour period range from 0.002 µg/m^3 in Quebec to 2 µg/m^3 in Manitoba and Newfoundland (Government of Alberta, 2016; Government of Manitoba, 2005; Ministère du Développement durable & de l'Environnement et de la Lutte contre les changements climatiques, 2016; Newfoundland and Labrador, 2004; Ontario Ministry of the Environment, 2012). The hazardous air pollutants included in guidelines are not

[4] British Columbia, Alberta, Manitoba, Ontario, Québec, Newfoundland and Labrador

consistent throughout the provinces as well; B.C. Ambient Air Quality Objectives list only 7 contaminants, while Ontario and Quebec guidelines provide the criteria for more than 300 air pollutants. On the other hand, the guidelines for crude concentration of total PM are generally promulgated with the same guideline values; all jurisdictions adopted Canada Wide Standard for $PM_{2.5}$ of 30 $\mu g/m^3$ in a 24-hour period. This indicates that establishment of federal standards as a ground rule is indispensable to achieve consistent guidelines across Canada. Some countries monitor more comprehensive PM components in air than Canada at national level. United Kingdom and United States both require monitoring of lead in ambient air for national air quality guidelines (Department for Environment Food and Rural Affairs, 2012; US Environmental Protection Agency, 2008). European legislation has adopted the new Air Quality Framework Directive in 2008, stating a requirement to measure the composition of PM from at least one site, which enables metal analysis in ambient air (Quincey & Butterfield, 2009).

For occupational health, the frequency, duration, concentration, and route of exposure are not in the same manner as the exposures in environmental health, and the population at risk is precise; therefore, guidelines or regulations are generally more specific and detailed to prevent adverse health effects. Population at risk is usually limited to those who work at or live around the occupational sites. The route of exposure relies on the occupational settings, but exposures are usually via inhalation and occasionally through the skin. Exposures at work occur at much greater concentrations compared to environmental exposure over a given period; on the other hand, the duration of total exposure taken into consideration is shorter than environmental exposure. It is easier to track the frequency and duration of exposure because workers and employers usually record the hours of work. The level of exposure may be a lot higher than

environmental exposure, which demands moderately sensitive measuring techniques to measure the exposure. Consequently, unlike environmental exposure assessment that requires more sensitive measuring instruments, occupational exposure can be assessed with simple and well-validated techniques (Semple, 2005). Occupational air quality regulations are in time-weighted average (TWA) for a specific period which is 8 or 10 hours to state permissible exposure limits (PEL), recommended exposure limits (REL), or threshold limit values (TLV); or 15-minute or 30-minute exposure average for short-term exposure limits (STEL), depending on regulatory agencies (Association Advancing Occupational and Environmental Health, n.d.; National Institute for Occupational Safety and Health, n.d.; United States Department of Labor, n.d.; Worksafe BC, 2015). Occupational guidelines generally have more detailed criteria of hazardous chemicals than ambient air quality guidelines. However, it should be noted that most regulatory limits of occupational air quality objectives are based on oral-to-inhalation extrapolation because route-specific toxicity data for inhalation exposure is insufficient due to a lack of studies (Rennen et al., 2004). This implies that the limitations of RtR extrapolation will prominently influence the appropriateness of guidelines.

The needs to regulate the metal components of particulate matters

Currently, most air quality guidelines for health purposes simply monitor the total mass concentration of PM due to administrative and financial constraints and limited number of sample collection sites. When air pollution is discussed, it is often focused only on the total concentration of PM, even though PM consists of various components, collectively categorized by the size. Studies have called attention to the fact that crude measurements of PM are not sufficient to observe the epidemiology of the adverse health effects attributable to airborne

exposure because some components of PM are more associated with and responsible for certain adverse health effects (Lippmann, 2010, 2012; Quincey & Butterfield, 2009). When components of $PM_{2.5}$ were examined for their influences on the daily mortality associated with $PM_{2.5}$, it was found that certain chemical components, namely aluminum, arsenic, nickel, sulfate, and silicon, significantly increased the mortality rates modification effects (Franklin, Koutrakis, & Schwartz, 2008). Monitoring and studying chemical components of PM and their effects will enable targeted regulations on the most toxic components with cost-effective methods. For example, since aluminum and nickel are the significant effect modifiers of mortality due to residual oil fly ash[5], monitoring and regulation may be focused to those two components (Franklin et al., 2008). Therefore, it is important to identify the most toxic components to adopt more effective health policies.

Air pollution is associated with numerous adverse health outcomes from allergies to lung cancer; however, there are no clear criteria of research methodology advising what specific components need to be measured to examine health effects attributable to air pollution. Escalating attention on traffic and fossil fuel combustion-related pollution, with increasing number of motor vehicles and their highly variable PM composition which may result in acute exposure, brings a need to analyze the metal components of PM (Lippmann, 2010; Lippmann & Chen, 2009). Toxic metals can result in various adverse health effects; Table 1 below describes some of the common toxic metals and the corresponding health risks (Agency for Toxic Substances and Disease Registry, n.d.; Järup, 2003).

[5] A component of ambient particulate matter which consists of iron, aluminum, vanadium, nickel, carbon, and zinc

Table 1. Summary of common toxic metals and the health effects of acute and chronic exposure via various routes

METALS	HEALTH EFFECTS
Aluminum[a]	Impaired lung function, fibrosis, impaired neurobehavioral function, sensory function, and cognitive function
Arsenic[a,b]	Nausea, vomiting, diarrhea, irritation, cardiovascular effects, encephalopathy, irritation, skin cancer, peripheral neuropathy, bladder cancer, lung cancer
Beryllium[a]	Respiratory damage (nasopharyngitis, shortness of breath, labored breathing, chemical pneumonitis), gastrointestinal damage, fibrosis, irritation, lung cancer
Cadmium[a,b]	Kidney damage, lung damage, decreased lung function, decreases in bone mineralization, increased risk of bone fractures, emphysema, lung cancer
Chromium (VI)[a]	Respiratory and gastrointestinal irritation, altered pulmonary function, hemolysis, kidney failure, damaged reproductive systems, fibrosis, lung cancer
Lead[a,b]	Decreased activity of Hematological enzymes, elevated blood pressure, kidney failure, reduced reproductive systems, neurological impairment (encephalopathy, peripheral neuropathy, neurobehavioral and neuropsychological effects in adults, cognitive and neurobehavioral effects in children)
Mercury[a,b]	Diarrhea, fever, vomiting, nausea, gastrointestinal, kidney, muscular, cardiovascular, and neurological damages (anxiety, tremor)

[a] Agency for Toxic Substances and Disease Registry, n.d. ; [b] Järup, 2003

As shown above, the range and severity of health effects vary depending on the metal in question, and certainly, they are not limited to those listed above. However, despite the importance of metal component monitoring in PM, neither the federal air quality guideline nor the current B.C. Ambient Air Quality Objectives have detailed criteria for metal dusts (British Columbia Ministry of Environment, 2016; Environment Canada, 2013). In addition, as mentioned in the previous section, not all guidelines have sufficiently described metal dusts

criteria for ambient air. Therefore, there is a necessity to include constant monitoring and control of metal components of PM with adequate criteria to better protect the population.

Risk assessments on metal dusts in ambient air and occupational settings

To set the criteria of metal components in PM for air quality guidelines, health risks of metal dusts in air should be assessed first. When searched for background reviews, only a handful of published articles are found on risk assessment of exposure to metal dusts in ambient air, mostly in Asia where ambient air pollution is severe, possibly due to the complexity linked to such risk assessments and the purpose which is usually regulatory or administrative rather than academic. Commonly studied heavy metals for exposure assessment of ambient air are lead, copper, zinc, arsenic, and cadmium along with iron, vanadium, chromium, manganese, cobalt, and nickel. These assessments were conducted around densely populated areas and industrial sites mostly in Asia for health outcomes such as cancer and neurobehavioral disorders (Cheng et al., 2017; Kong et al., 2012; Singh & Gupta, 2016; Tan et al., 2014). Some studies were conducted in New York City, assessing inhalation exposures resulting from the collapse of the World Trade Center towers (Lorber et al., 2007) and exterior lead dust (Caravanos, Weiss, Blaise, & Jaeger, 2006). One study was undertaken in Germany, finding platinum group metal particles in PM from traffic exhausts are present not only in areas close to the roads, but also in areas far from the sources (Zereini et al., 2001). The risk assessments of metal dusts in ambient air published in academic database do not cover enough environmental settings to draw conclusions which toxic metal is of the most concern.

Risk assessment of heavy metal dusts in occupational settings is less complicated than ambient air as the source is often clear. Most of the studies are assessing welding, mining, and chemical

production industries. Sometimes, relationships of exposure and specific health outcomes are assessed; a literature review on the association between exposure to manganese dusts in welding industries and neurological disease such as Parkinson's disease found that epidemiological evidence is not clear to conclude the causality (Flynn & Susi, 2009). Several models can be developed to take environmental exposure into account. A study on exposure to hexavalent chromium attributable to lung cancer in the chromate industry developed 6 exposure-response models to evaluate the exposure including smoking (Park et al., 2004). Analytical cross-sectional study may prove to be beneficial in finding a linkage between the exposure and non-specific symptoms; a study on exposure to metal dusts among brass workers in Sri Lanka indicates that the prevalence of non-specific symptoms is higher with metal dust exposure, calling actions for preventive measures (Jayawardana, 2004). One interesting study was conducted at auto body shops in Nigeria, where imported used auto vehicle market is growing, on the exposure to lead, manganese, and copper from car paint dusts, concluding that chronic exposure to car paint dusts may lead to adverse health outcomes including cancers (Nduka, Onyenezi Amuka, Onwuka, Udowelle, & Orisakwe, 2016). Another study, assessing the occupational exposure of urban public bus drivers to trace metals in gas emissions from buses, quantified the concentration of specific metal dusts, mainly zinc, lead, and copper to conclude that there is a potential carcinogenic risk (Gao et al., 2015). Similar to ambient air risk assessment, not many risk assessments were found in academic database, perhaps because the purpose of such risk assessments is usually regulatory or administrative rather than academic.

Limited ambient air criteria for metal dusts in Canada

In Canada, National Air Pollution Surveillance (NAPS) program, established in 1969 initially focusing on sulfur dioxide and PM, measures 340 air toxics including heavy metals to provide a uniform Canada-wide air quality database. The heavy metals that are tracked include selenium, nickel, manganese, lead, cobalt, chromium, cadmium, beryllium, arsenic, and antimony; but not all toxic metals are monitored by NAPS. One study assessed NAPS monitored air toxics and compared the concentrations with the air quality guideline standards of Canadian jurisdictions (Galarneau et al., 2016). It was found that many metal pollutants have exceeded or approached at least one guideline. It should be noted that this is only based on $PM_{2.5}$ whereas most metal dusts are expected to be present in coarser PM_{10}; therefore, the reported measurements are likely to be underestimated.(Galarneau et al., 2016). As mentioned above, many guidelines do not have complete criteria of ambient air metal concentrations. For an effective ambient air metal dust management, it is imperative to include such standards in the guidelines.

Health effects to vulnerable populations

A comprehensive air quality guideline should consider vulnerable populations such as pregnant women, children, elderly, and those with pre-existing medical conditions. Vulnerable populations may be more sensitive to the risks of air pollution, resulting in exacerbated adverse health effects; therefore, air quality guideline is desired to be sufficiently protective.

Studies suggest that maternal exposure to ambient air pollution during pregnancy, particularly in the early-stages, is associated with various adverse birth outcomes of fetuses and infants (Estarlich et al., 2016; Laurent et al., 2016; Lavigne et al., 2017; Liang, Wu, Fan, & Zhao, 2014; S. Liu, Krewski, Shi, Chen, & Burnett, 2007; Malley et al., 2017; World Health Organization, 2017a;

Yao et al., 2016). The adverse effects of air pollution on birth outcomes are preterm birth, low birth weight, birth defects, childhood respiratory mortality, intrauterine growth retardation, and even early childhood cancers. However, the strength of associations between each birth outcome and air pollution varies. A systemic review on ambient air pollution and pregnancy outcomes revealed that there was a strong evidence to infer a causal relationship between air pollution and premature death in early childhood due to respiratory problems (Srám, Binková, Dejmek, & Bobak, 2005). The evidences to support the causality of air pollution to birth weight, preterm birth, and intrauterine growth retardation were not sufficient, requiring further research. However, molecular epidemiologic studies suggested biological mechanisms supporting the potential association of those birth outcomes to air pollution (Srám et al., 2005). The association of birth defects and air pollution was not significant. The reviewers described that particulates seem to be the most important pollutant for infant mortality; however, lack of availability of the precise pollutant composition limited the confidence of their conclusion. This, again, emphasizes the need of monitoring PM components.

The exposure to ambient air pollution in young children is more problematic than adults due to their physiological susceptibility such as rapid neurological development and higher ratio of body surface area to volume leading to greater health risk; children under 2 years of age have toxicokinetic mechanism differences from adults, having much longer half-lives of some metabolites as well as their parent compounds (Falk-filipsson, Hanberg, Victorin, Warholm, & Walle, 2007). In addition, the behavioural characteristics, for instance, extended periods of time spent outdoors during daily peak times of air pollution, may increase the level of exposure. Ambient air pollution plays a significant role in the development of chronic respiratory diseases,

asthma, congenital anomalies, cardiovascular disease, diabetes, and cancers in early childhood (Lacasaña, Esplugues, & Ballester, 2005; World Health Organization, 2017b). Also, neurological and behavioural disorders have been associated with air pollution, possibly due to the heavy metal components in ambient air; studies identify air pollutants as neurotoxins resulting in disorders such as attention-deficit hyperactivity disorder and schizophrenia, which have life-long effects on children (Min & Min, 2017; Pedersen, Raaschou-Nielsen, Hertel, & Mortensen, 2004; Siddique & Banerjee, 2011).

Elderly population and patients with existing medical conditions may be more susceptible to adverse health outcomes attributable to air pollution. It has been found that nickel is particularly influential to those sensitive to cardiac responses. Special attention is advised on both nickel and vanadium, which are most closely associated with residual oil combustion, for their health impacts on acute and chronic respiratory and cardiovascular diseases (Lippmann & Chen, 2009). One study emphasizes that ambient air pollution at levels below the air quality guidelines is associated with the mortality and morbidity of chronic obstructive pulmonary disease (COPD), and improvement of guidelines is imperative to protect the patients (Y. Liu et al., 2016). PM_{10} in ambient air is associated with increased emergency visits for asthma, especially for the patients with a prior history of allergic rhinitis or atopic dermatitis (Noh et al., 2016). The risk of air pollutant exposure may be much higher when pregnant mothers have pre-existing medical conditions, for both the fetus and the mother. A study found a substantial association of preterm birth with traffic-related air pollution in women with asthma (Mendola et al., 2016).

Overview of Route-to-route Extrapolation Guidelines

Application of route-to-route extrapolation

If heavy metal dusts in air are required to be controlled, what values should be established as standards? It is ideal to use the data of the same route of exposure, which is inhalation. However, due to the limited database of inhalation toxicity studies, the limits are often based on oral toxicity data, extrapolated from oral to inhalation toxicity level (Rennen et al., 2004). It is a traditional approach to use RtR extrapolation in risk assessments when route-specific data is not available, due to number of reasons. Interdepartmental Group on Health Risks from Chemicals (IGHRC) states in their draft guidelines on RtR extrapolation that the practical convenience of oral studies and complexity of inhalation exposure bring a pragmatic necessity to extrapolate toxicity data to assess human health risks via inhalation (Interdepartmental Group on Health Risks from Chemicals, 2005).

Most of toxicity studies are undertaken using oral exposure because it is more straightforward to conduct and interpret than other routes with quantifiable dosimetry, especially by gavage, unless the examined chemicals are gases or highly volatile organic liquids (Interdepartmental Group on Health Risks from Chemicals, 2005). Also, oral exposure is likely to be less stressful for test animals particularly on acute toxicity, so it curtails ethical issues with animal studies. By excluding animal inhalation or dermal studies, it resolves time and financial constraints as well. Therefore, this brings a need of extrapolation from readily available oral data to estimate inhalation toxicity.

Another substantial issue springs from the complexity of inhalation exposure. In addition to concentration and duration of exposure that are also considered in estimation of oral exposure,

the size of inhaled particles affects the sites of absorption at different part of respiratory tract. Coarse particles will only reach the upper respiratory tract whereas fine particles are able to penetrate deeper in lung to the alveoli. Other factors that influence the inhalation toxicity are solubility and reactivity of chemicals at lung tissue as well as physiological aspects such as lung capacity and breathing rate (Falk-filipsson et al., 2007; Interdepartmental Group on Health Risks from Chemicals, 2005; Pauluhn, 2003). All these additional factors must be considered to accurately estimate the dose of inhalation exposure, and obstruct inhalation exposure studies.

However, RtR extrapolation has significant general limitations. The problems are mainly due to unavailability of data on toxicokinetics and effects of local toxicity. Toxicokinetic information on distribution, metabolism, and excretion is largely missing for inhalation exposure, which obstructs the true comparison of effective doses via ingestion and inhalation at target organs. Absorption factor is seldom available as well, but more obtainable than distribution or excretion. Some studies indicate that toxicokinetic data on absorption at least should be available to make reliable RtR extrapolation (Bessems & Geraets, 2013; Falk-filipsson et al., 2007; Geraets, Bessems, Zeilmaker, & Bos, 2014; Interdepartmental Group on Health Risks from Chemicals, 2005; Schröder et al., 2016), as the absorption of chemicals will determine the target organ dosage. However, as it is mentioned for inhalation, the absorption via lung is vastly variable to that of oral absorption, depending on the physical and chemical properties. Absorption at alveoli leads to direct systemic circulation, passing through the heart into general circulation before reaching the liver for metabolism (Interdepartmental Group on Health Risks from Chemicals, 2005; Pauluhn, 2003). Diffusion relies on solubility. Thus, absorption factors cannot be determined without knowing the physical and chemical nature of substances, and

factors affecting absorption through inhalation differ from those for ingestion (Naumann et al., 2009). Furthermore, if direct effect at the site of exposure leading to local toxicity is present, RtR extrapolation would not be appropriate because it is to estimate systemic toxicity, not taking local effect into account (Falk-filipsson et al., 2007; Geraets et al., 2014; Pauluhn, 2003). In addition, high reactivity leading to local toxicity reduces the amount of absorption (Interdepartmental Group on Health Risks from Chemicals, 2005). If a chemical has a first pass effect[6] after ingestion, this may decrease the absorption. In that case, respiratory exposure, which does not go through first pass effect, will result in larger absorbed doses even with the same amount of exposure. If RtR extrapolation is used for these types of chemicals, the extrapolated value will consequently be underestimated (Falk-filipsson et al., 2007; Rennen et al., 2004).

These limitations, mainly from limited amount of experimental data, hinder the reliability of RtR extrapolation and validation of definite conclusions. More studies are needed to build sufficient database that extrapolation can be based upon; however, this will take time and until then, extra caution must be taken when performing RtR extrapolation. Therefore, it is advised to take meticulous approaches to RtR extrapolation with assessment factors and repeated dose toxicity studies (Geraets et al., 2014; Interdepartmental Group on Health Risks from Chemicals, 2005).

Criteria of route-to-route extrapolation and guidance

Number of studies suggest the prerequisites to perform reliable RtR extrapolation (Geraets et al., 2014; Pepelko & Withey, 1985; Rennen et al., 2004). The *Guidelines on Route-To-Route*

[6] If the parent compound is responsible for toxicity, the effective dose reduces greatly when orally administered compounds are absorbed by the gastro-intestinal tract, enter the liver, and go through metabolism before reaching the systemic circulation (Interdepartmental Group on Health Risks from Chemicals, 2005)

Extrapolation of Toxicity Data When Assessing Health Risks of Chemicals (Interdepartmental Group on Health Risks from Chemicals, 2005) suggest the following criteria:

- Absorption is the same between routes, or the difference is known and can be quantified.
- The critical target tissue is not at the portal of entry of the compound (i.e. the concern is with systemic toxicity and not local effects).
- There is no significant metabolism of the chemical by oral, gut or skin enzymes or in pulmonary macrophages, nor transformation by other processes in the gut or lung.
- First-pass effects are minimal.
- The chemical is relatively soluble in body fluids.

It also gives further specific guidance on oral to inhalation extrapolation. As there are higher possibilities that inhalation toxicity is underestimated when it is extrapolated from oral to inhalation, it is advised to assume the bioavailability of inhalation exposure to be 100% unless the information is available. In reality, some portion of inhaled dust or gas is exhaled without absorption. Coarse particles that are inhalable but not respirable mostly remain in the upper respiratory tract and are then absorbed via gastro-intestinal tract after swallowing; this will not be problematic since it can be practiced the same as oral toxicity (Interdepartmental Group on Health Risks from Chemicals, 2005). However, respirable particles, which can reach far deeper into the lung, can be absorbed for extended periods of time and often do not have exact bioavailability data by inhalation. Further complicating the assessment, it is not quite realistic to

measure the sizes of particles and define what portion will be respirable for each and every case. Hence, to be precautious, it is conservative to assume the absorption of such particles is 100%.

To avoid the underestimation of inhalation toxicity for the substances with lower oral toxicity, it is suggested to assume 10% oral bioavailability and 100% bioavailability by the inhalation route, and 50% oral bioavailability and 100% bioavailability by the inhalation route for substances with high oral toxicity, when data on inhalation bioavailability is missing (Interdepartmental Group on Health Risks from Chemicals, 2005). Table 2 is adopted from the *Guidelines on Route-To-Route Extrapolation of Toxicity Data* to show the factors suggested by the guidelines.

Table 2. Factors for deriving a respirable RtR NOAEL from an oral NOAEL (adopted from *Guidelines on Route-To-Route Extrapolation of Toxicity Data*)

Data available in addition to oral toxicity data	**Multiply critical oral NOAEL by:**
Oral and inhalation bioavailability data	% oral absorption/% respirable absorption
Oral bioavailability; acute inhalation toxicity unknown	% oral absorption/100
Acute oral and inhalation toxicity data	Correction factor derived from a comparison of the relative potency in an acute oral toxicity study compared with an acute inhalation toxicity study.
Substance classified for acute oral toxicity as toxic or very toxic	
Bioavailability on inhalation	50/% bioavailability by the inhalation route
None	50/100
Substance classified for acute oral toxicity as harmful or not classified	
Bioavailability on inhalation	10/% bioavailability by the inhalation route
None	10/100

Adequacy of route-to-route extrapolation

Therefore, it is necessary to evaluate the adequacy of using RtR extrapolation for each practice and each substance since there is no uniform or default correction factor, as researchers repetitively state (Geraets et al., 2014; Hinderliter, Delorme, & Kennedy, 2006; Interdepartmental Group on Health Risks from Chemicals, 2005; Rennen et al., 2004). Quantitative estimation of errors is required to assess the discrepancy between oral and respiratory toxicity and evaluate the guidelines. Since most heavy metal dusts are not gases or volatile organic liquids, it is highly probable that the standards are established based on oral toxicity data. Current air quality guidelines are often missing this assessment of RtR application or not publicly available. This leads back to the purpose of this project: to assess if it is acceptable to use RtR extrapolation for such guidelines, to sufficiently protect the population's environmental and occupational health.

Methods

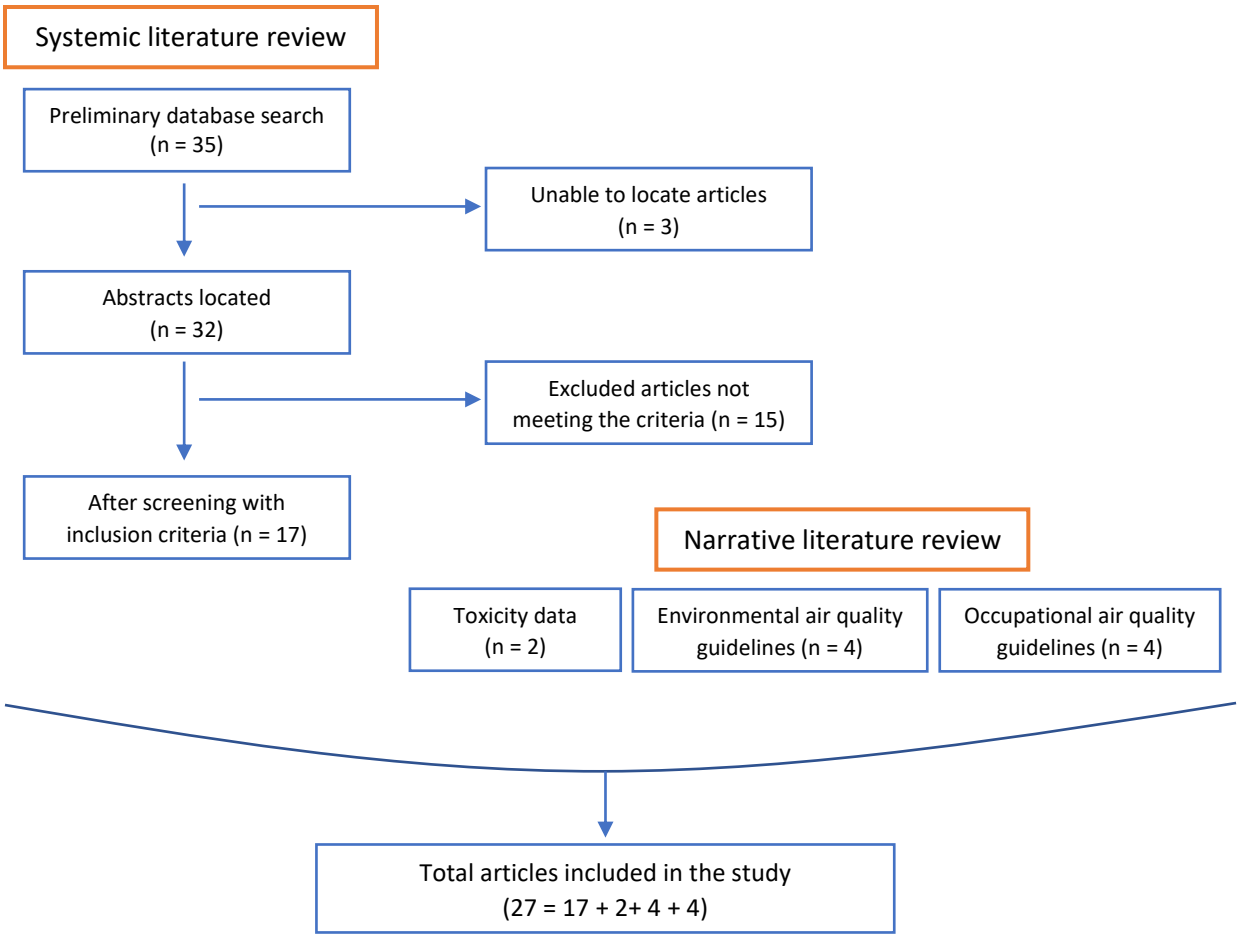
Data collection and sources

A systematic literature review using 'route-to-route extrapolation' as the search term was performed, using PubMed as the primary database. The initial systemic search returned 35 articles. I searched titles and abstracts with the inclusion criteria: 1) articles in English, 2) articles in peer reviewed journals, and 3) evaluation or model development for oral-to-inhalation extrapolation; after the screening based on the abstracts, I excluded 15 articles with additional 3 articles unable to be located, leaving 17 articles.

I also reviewed documents from regulatory agencies in the US and Canada to undertake a narrative review assessing the current state of application of RtR extrapolation in air quality

guidelines for environmental and occupational health purposes. No adequate federally managed Canadian toxicity database was found; thus, US databases were consulted for reference exposure limit values. Agency for Toxic Substances and Disease Registry (ATSDR) and United States Environmental Protection Agency Integrated Risk Information System (EPA IRIS) were used together as recognized surveillance data sources for reference oral exposure limit values, since they are complementary when values are only available in one database, and the data are mostly in agreement when present in both. If the values are not the same, ATSDR value was used. For ambient air quality guidelines, because there is no Canadian federal guideline addressing metal components, provincial air ambient quality guidelines from Ontario, Alberta, and Manitoba were referred, as well as US state guidelines from Texas as international guidelines for comparison. National Institute for Occupational Safety and Health (NIOSH), Occupational Safety and Health Administration (OSHA), Association Advancing Occupational and Environmental Health (ACGIH), and WorkSafeBC were consulted for occupational air quality guidelines. Minimal risk level(MRL) from ATSDR and reference dose (RfD) or reference concentration (RfC) values from EPA were collected to calculate RtR extrapolated limits to compare with governmental guidelines. The systemic review articles and the narrative review articles were collected together, and all the articles were closely reviewed.

Figure 1. Flow chart of search strategy of the literature review



Data description and synthesis

Oral and Inhalation exposure limit values were converted into daily dose based on body weight, volume of daily inhaled air, and average bioavailability considering percentage deposition in lungs, if known. The reference values of body weight, volume of daily inhaled air, and bioavailability are adopted from ATSDR (Agency for Toxic Substances and Disease Registry, 2005):

- Body Weight (BW) = 70kg (adult, approximate average)
- Daily Air Intake Rate (AR) = 20 m^3/day

Figure 2. Equations and standard default values to calculate exposure dose (adopted from ATSDR appendix G)

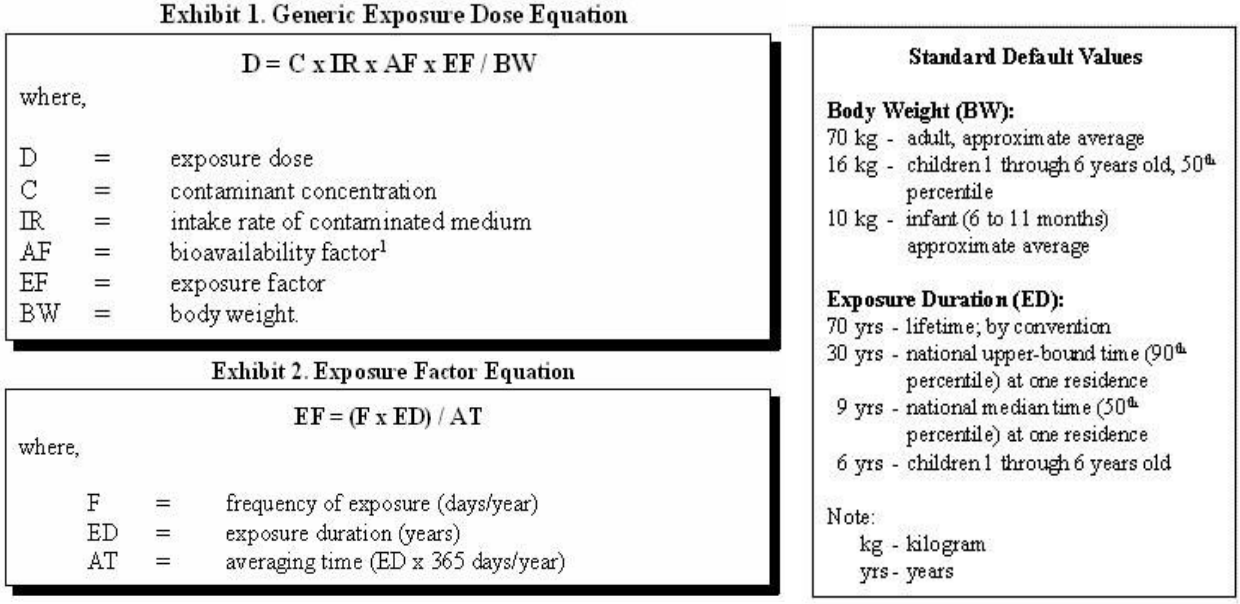


Exhibit 1. Generic Exposure Dose Equation

$$D = C \times IR \times AF \times EF / BW$$

where,

D	=	exposure dose
C	=	contaminant concentration
IR	=	intake rate of contaminated medium
AF	=	bioavailability factor[1]
EF	=	exposure factor
BW	=	body weight.

Exhibit 2. Exposure Factor Equation

$$EF = (F \times ED) / AT$$

where,

F	=	frequency of exposure (days/year)
ED	=	exposure duration (years)
AT	=	averaging time (ED x 365 days/year)

Standard Default Values

Body Weight (BW):
70 kg - adult, approximate average
16 kg - children 1 through 6 years old, 50th percentile
10 kg - infant (6 to 11 months) approximate average

Exposure Duration (ED):
70 yrs - lifetime; by convention
30 yrs - national upper-bound time (90th percentile) at one residence
9 yrs - national median time (50th percentile) at one residence
6 yrs - children 1 through 6 years old

Note:
kg - kilogram
yrs - years

I developed my own formula for calculation for this project, based on the equations provided by ATSDR in Figure 2. The formula is shown below:

$$\text{Oral dose (mg/day)} = \text{Oral exposure limit (mg/kg/day)} \times \text{BW (kg)}$$

$$\text{Inhalation dose (mg/day)} = \text{Oral dose (mg/day)} \times \frac{\text{Oral bioavailability (\%)}}{\text{Respiratory bioavailability (\%)}}$$

$$\text{Inhalation RtR limit}^{7}\ (\text{mg/m}^3) = \frac{\text{Inhalation dose (mg/day)}}{\text{Daily Air Intake Rate (m}^3\text{/day)}}$$

This calculated inhalation RtR limits were compared to available inhalation MRL or RfC provided by ATSDR or EPA. The RtR limits were compared to the guideline values as well. To clearly demonstrate the difference between RtR limits and guidelines with the same duration of exposure, acute and chronic exposure RtR limits were compared to ambient air quality guidelines of Ontario and Texas for 24-hour and annual values, respectively.

[7] RtR limits are calculated values that are extrapolated from oral to inhalation exposure limits in this document

Results

Systemic review of oral-to-inhalation extrapolation

Table 3 shows the summary of systemic review. Out of 17 reviewed articles, 8 articles are applicable to risk assessment or risk characterization. Ten articles developed physiologically based pharmacokinetic (PBPK) modeling which can potentially be used in toxicity studies, and most of the studies are based on rat data. One study (Shankaran, Adeshina, & Teeguarden, 2013) developed PBPK model using human toxicokinetic data, which gets rid of the uncertainty due to inter-species extrapolation. Some studies (Borghoff, Parkinson, & Leavens, 2010; Himmelstein et al., 2012; Hinderliter et al., 2006) found gender differences in metabolism and exhalation rates, resulting in inconsistent extrapolation factors between male and female. A number of articles, mostly on PBPK model development, suggest that reliable RtR extrapolation is achievable. However, some state the prerequisites for RtR reliability, including absence of direct toxicity and available toxicokinetic data. The articles expressing concerns with the reliability of RtR emphasize that case-by-case extrapolation adjustment factor[8] is required along with application only to systemic toxicity, although it is acknowledged that RtR is pragmatic with limited dataset of inhalation toxicity (Falk-filipsson et al., 2007; Pauluhn, 2003). Many articles suggest dosimetry or extrapolation adjustment factor for the extrapolation, either from the PBPK models or conclusion of article reviews. Since many PBPK studies provide the adjustment factor based on chemical-specific scientific evidences, review articles chose to be conservative with adjustment factors to minimize underestimation of toxicity. Most exposure studies examined acute and sub-acute/sub-chronic exposures.

[8] A conversion factor for exposure limit from point of administration (often oral) to another route of exposure (i.e. inhalation) with the equipotent dose

Table 3. Summary of systemically reviewed articles

THEME	JOURNAL ARTICLES
Risk Assessment	Bessems & Geraets, 2013; Falk-filipsson et al., 2007; Geraets et al., 2014; Naumann et al., 2009; Pauluhn, 2003; Pepelko & Withey, 1985; Rennen et al., 2004; Schröder et al., 2016
Physiologically based pharmacokinetic (PBPK) modeling	
Rat data	Arts et al., 2004; Borghoff et al., 2010; Clewell et al., 2001; Himmelstein et al., 2012; Hinderliter et al., 2006; Naumann et al., 2009; Sweeney & Gargas, 2016; Sweeney, Saghir, & Gargas, 2008
Human data	Shankaran et al., 2013
Simpler steady-state model development	Chiu & White, 2006
Gender difference found	Borghoff et al., 2010; Himmelstein et al., 2012; Hinderliter et al., 2006
Does it suggest RtR is reliable?	
Yes	Chiu & White, 2006; Hinderliter et al., 2006; Shankaran et al., 2013; Sweeney & Gargas, 2016; Sweeney et al., 2008
Yes, with conditions	Arts et al., 2004; Bessems & Geraets, 2013; Borghoff et al., 2010; Pepelko & Withey, 1985
No	Falk-filipsson et al., 2007; Pauluhn, 2003; Rennen et al., 2004
Dosimetry or adjustment factor provided by authors	Arts et al., 2004; Borghoff et al., 2010; Chiu & White, 2006; Clewell et al., 2001; Falk-filipsson et al., 2007; Geraets et al., 2014; Himmelstein et al., 2012; Hinderliter et al., 2006; Naumann et al., 2009; Schröder et al., 2016; Shankaran et al., 2013; Sweeney & Gargas, 2016; Sweeney et al., 2008
Is it conservative in absorption via inhalation?	Geraets et al., 2014; Schröder et al., 2016; Sweeney & Gargas, 2016
Duration of exposure	
Acute	Clewell et al., 2001; Himmelstein et al., 2012; Hinderliter et al., 2006; Naumann et al., 2009; Shankaran et al., 2013
Sub-acute/sub-chronic	Arts et al., 2004; Borghoff et al., 2010; Clewell et al., 2001; Sweeney & Gargas, 2016
Chronic	Clewell et al., 2001; Sweeney & Gargas, 2016

Most studies recognize RtR extrapolation as a fairly reliable method for risk assessment although there are certain conditions to be satisfied, such as availability of toxicokinetic data and absence of local toxicity. The studies that do not agree on the reliability express their concerns on these prerequisites and suggest adjustment with case-by-case extrapolation factors. The reliability of RtR extrapolation significantly depends on the availability of toxicokinetic data; therefore, more route-specific studies are necessary to enhance the database.

Most experimental studies are based on PBPK model using rats, since rats have shorter lifespan to study chronic health effects. However, despite this advantage, many studies examined acute and sub-acute exposures only. This may be due to time and financial constrains as well as the fact that acute exposure is considered more important to be studied. Further reproductive toxicity studies on multiple generations with pregnant rats might be necessary as pregnant women may be at greater risks which will affect the child.

Intriguingly, not many studies considered a conservative approach in inhalation absorption. For empirical studies, they provide case-specific experiment-based extrapolation factors. A possible explanation for others is that the primary purpose of RtR extrapolation is to extrapolate NOAEL to assess human health risks in practical way. When too precautious in practice, it might lose the benefit of RtR extrapolation by overestimating toxicity.

Comparison of guidelines and extrapolated values of inhalation exposure limit from reference oral limit

After reviewing literature for various perspectives toward RtR extrapolation, the reference oral exposure limit values from ATSDR and EPA IRIS were extrapolated to inhalation RtR limits to be

scrutinized with current air quality guidelines. The list of references and guidelines is shown in Table 4 below. The MRL database from ATSDR is more comprehensive than RfD database from EPA; however, as a lot of them are the same, when one value is missing in ATSDR, EPA RfD was considered as chronic MRL for calculation.

Table 4. Summary of narratively reviewed articles

	ARTICLES
Reference for Exposure limits	Agency for Toxic Substances and Disease Registry, n.d.; US Environmental Protection Agency, n.d.
Ambient Air Quality Guidelines	Government of Alberta, 2016; Government of Manitoba, 2005; Ontario Ministry of the Environment, 2012; Texas Commission on Environmental Quality, 2016
Occupational Air Quality Guidelines	Association Advancing Occupational and Environmental Health, n.d.; National Institute for Occupational Safety and Health, n.d.; United States Department of Labor, n.d.; Worksafe BC, 2015

I extrapolated each oral exposure limit value from ATSDR and EPA into inhalation RtR limit value using the formula described in the methods section. A sample calculation with aluminum is shown below.

Oral dose = 1 mg Al/kg/day (chronic) × 70 kg = 70 mg/day

Inhalation dose = 70 mg/day × $\frac{2.505\ \%}{1.75\ \%}$ = 100.2 mg Al/day

Inhalation RtR limit = $\frac{100.2\ \mathrm{mg/day}}{20\ \mathrm{m^3/day}}$ = 5.01 mg Al/m^3

The oral-to-inhalation extrapolated RtR limit is compared to inhalation exposure limit provided by ATSDR or EPA, upon availability. For certain chemicals, for example, Molybdenum, regulations do not exist since proposed limits are questioned due to inadequate supporting evidence. It shows that the extrapolated values are larger than the literature values, indicating

that RtR extrapolation leads to underestimation of toxicity. Table 5 shows the oral-to-inhalation extrapolated RtR limit values compared to inhalation exposure limits based on studies; as not all values are available, only those that can be found are listed.

Table 5. Oral-to-inhalation RtR limits compared to experiment-based inhalation exposure limits

Metal	extrapolated RtR limit (µg/m^3)			Experiment-based Inhalation exposure limit (µg/m^3)		
	acute	intermediate	chronic	acute	intermediate	chronic
Beryllium			0.035			0.020*
Boron‡	606	606	606*	300		
Cadmium‡		0.385	0.077	0.030		0.010
Chromium metal‡						
Cr(III), insoluble			375*		5.00	
Cr(III), soluble					0.100	
Cr(VI), Particulates		2.54	0.457		0.300	0.100*
Cr(VI), aerosol		2.54	0.457		0.005	0.005
Cobalt‡		26.8			0.300	
Manganese			19.6*			0.300
Nickel‡			89.1*		0.200	0.090
Vanadium‡		4.03		0.800		0.100

*values from EPA; extrapolated RtR limits derived from RfD or experiment-based RfC directly referenced from EPA;
‡Direct respiratory toxicity

The oral-to-inhalation extrapolated RtR limits were also compared to ambient air quality guidelines as well as occupational guidelines. Figure 3 and 4 illustrate the results in graphs, and the results are shown in Table 6 and 7 for ambient and occupational air quality guidelines, respectively.

In order to clearly visualize the discrepancy between the extrapolated RtR limits and guideline values in the same duration of exposure, values are normalized to the RtR limit values in graphs. Figure 5 and 6 illustrate the results with Ontario Ambient Air Criteria (AAC) and Texas Air Monitoring Comparison Values (AMCC).

Figure 3. Comparison of Ambient Air Quality Guidelines Values to Calculated RtR limits

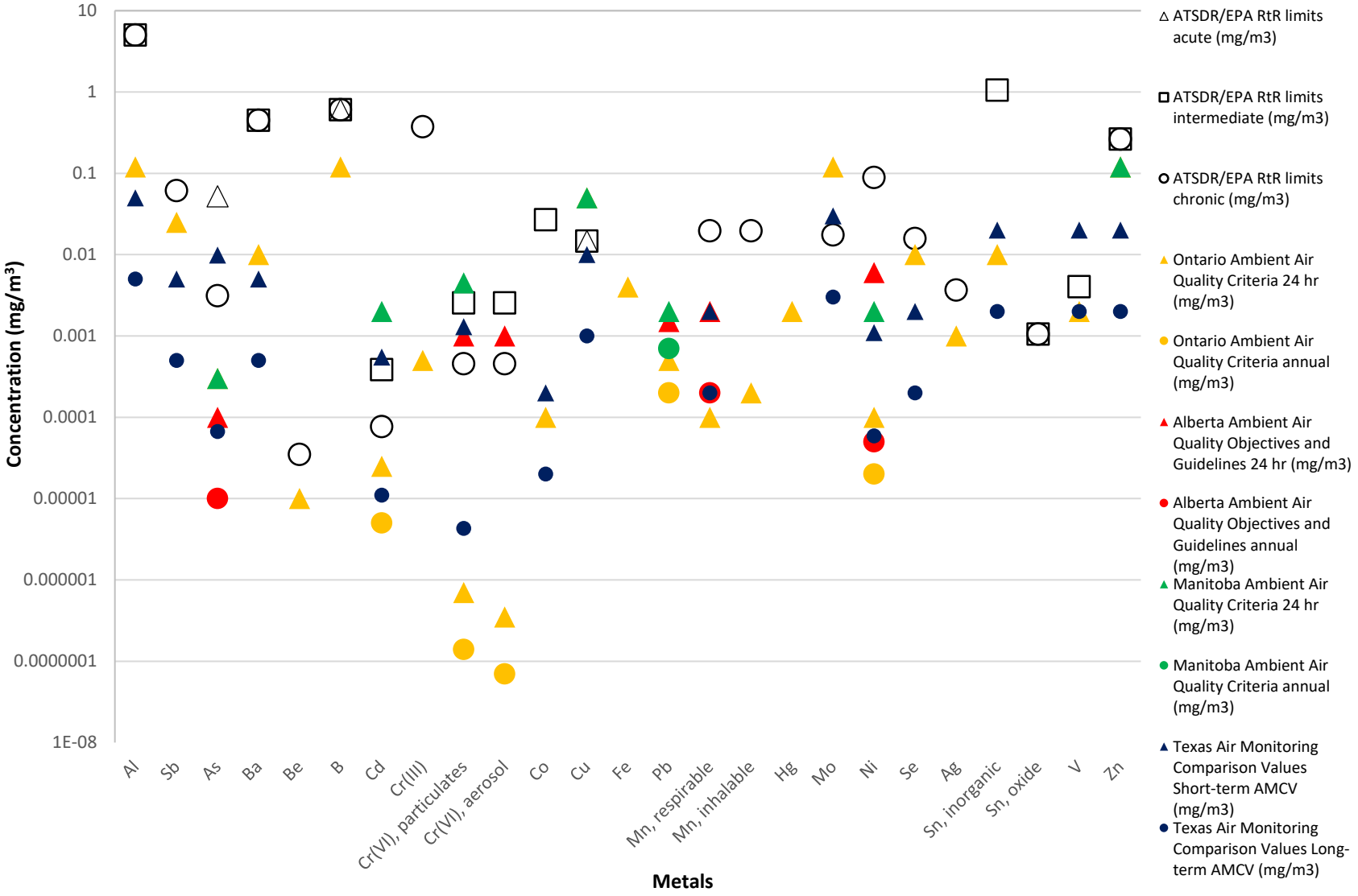


Figure 4. Comparison of Occupational Air Quality Guidelines Values to Calculated RtR limits

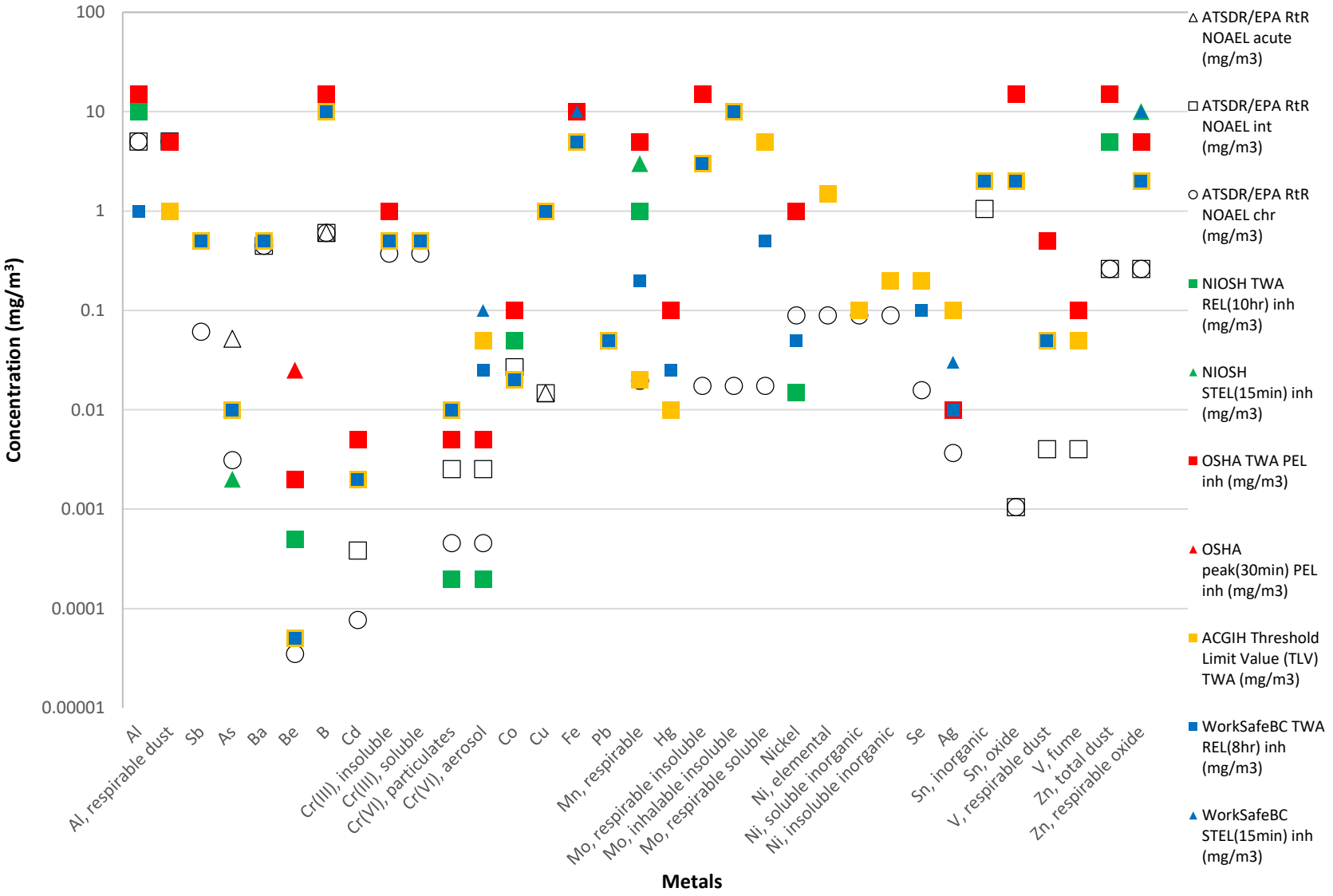


Table 6. Oral-to-inhalation extrapolated RtR limits compared to ambient air quality guidelines

Metals	extrapolated RtR limits (ug/m³)			Ontario Ambient Air Quality Criteria		Alberta Ambient Air Quality Objectives and Guidelines		Manitoba Ambient Air Quality Criteria		Texas Air Monitoring Comparison Values	
	Acute	Intermediate	Chronic	24 hr(ug/m³)	annual(ug/m³)	24 hr(ug/m³)	annual(ug/m³)	24 hr(ug/m³)	annual(ug/m³)	Short-term AMCV(ug/m³)†	Long-term AMCV(ug/m³)†
Aluminum		5010	5010	120						50	5
Antimony‡			61.3*	25						5	0.5
Arsenic	52		3.1	0.3		0.1	0.01	0.3		9.9	0.067
Barium		448	448	10						5	0.5
Beryllium				0.01							
Boron‡	606	606	606*	120							
Cadmium‡		0.4	0.1	0.025	0.005			0.002		0.55	0.011
Chromium metal‡											
Cr(III), insoluble			375*	0.5							
Cr(III), soluble				0.5							
Cr(VI), Particulates		2.5	0.5	0.0007	0.00014	1		4.5		1.3	0.0043
Cr(VI), aerosol		2.5	0.5	0.00035	0.00007	1					
Cobalt‡		26.8		0.1						0.2	0.02
Copper, dust‡	14.7	14.7		50				50		10	1
Iron oxide, fume				4							
Lead				0.5	0.2	1.5		2	0.7		
Manganese, respirable			19.6*	0.1		2	0.2			2	0.2
Manganese, inhalable				0.2							
Mercury, metallic‡				2							
Molybdenum			17.5*	120						30	3
Nickel‡			89.1*	0.1	0.02	6	0.05	2		1.1	0.059
Selenium‡			15.8	10						2	0.2
Silver‡			3.7*	1							
Tin, inorganic‡		1050		10						20	2
Tin Oxide		1.1	1.1								
Vanadium, oxide, respirable dust‡		4.0	0.0	2						20	2
Zinc, total dust‡		5010	5010	120						50	5

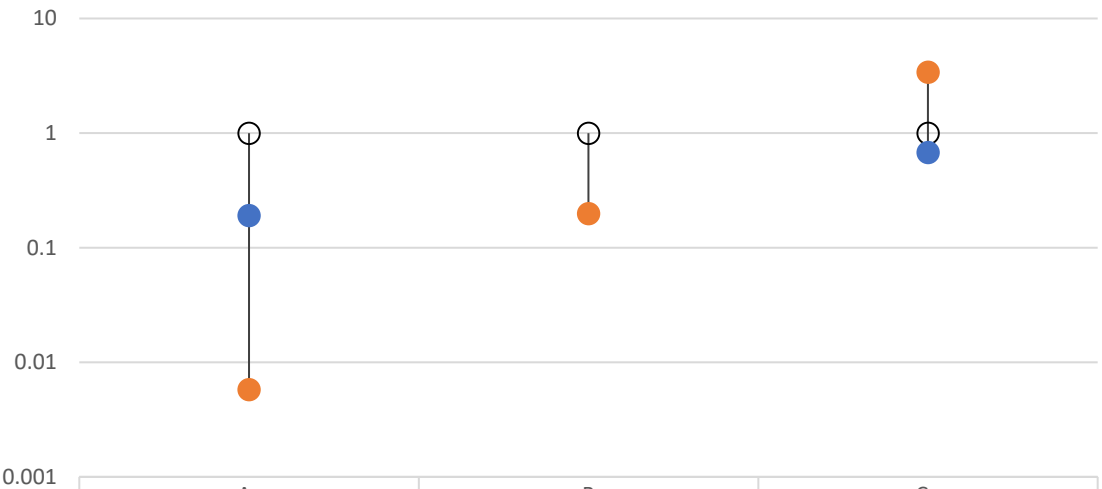
*Values from EPA: extrapolated RtR limits derived from RfD; †Air Monitoring Comparison Values; ‡Direct respiratory toxicity

Table 7. Oral-to-inhalation extrapolated RtR limits compared to occupational air quality guidelines

Metals	extrapolated RtR limits (mg/m³)			NIOSH[a]		OSHA[b]		ACGIH[c]	WorkSafeBC[d]	
	Acute	Intermediate	Chronic	TWA REL (mg/m³)	STEL (mg/m₃)	TWA PEL (mg/m³)	Peak PEL (mg/m³)	TLV TWA (mg/m³)	TWA REL (mg/m³)	STEL (mg/m³)
Aluminum		5.01	5.01	10		15			1	
respirable dust				5		5		1		
Antimony‡			0.0613*	0.5		0.5		0.5	0.5	
Arsenic	0.0520		0.00312		0.002	0.01		0.01	0.01	
Barium		0.448	0.448	0.5		0.5		0.5	0.5	
Beryllium			0.000035	0.0005		0.002	0.025	0.00005	0.00005	
Boron‡	0.606	0.606	0.606*	10		15		10	10	
Cadmium‡		0.000385	0.000077	LOWEST AS POSSIBLE		0.005		0.002	0.002	
Chromium metal‡										
Cr(III), insoluble			0.375*	0.5		1		0.5	0.5	
Cr(III), soluble				0.5		0.5		0.5	0.5	
Cr(VI), Particulates		0.00254	0.000457	0.0002		0.005		0.01	0.01	
Cr(VI), aerosol		0.00254	0.000457	0.0002		0.005		0.05	0.025	0.1
Cobalt‡		0.0268		0.05		0.1		0.02	0.02	
Copper, dust‡	0.0147	0.0147		1		1		1	1	
Iron oxide, fume				5		10		5	5	10
Lead				0.05		0.05		0.05	0.05	
Manganese, respirable			0.0196*	1	3	5		0.02	0.2	
Manganese, inhalable								0.1		
Mercury, metallic‡				0.1		0.1		0.01	0.025	
Molybdenum			0.0175*							
Insoluble, Respirable						15		3	3	
Insoluble, Inhalable								10	10	
Soluble, Respirable				5		5		5	0.5	
Nickel‡			0.0891*	0.015		1			0.05	
Elemental, inhalable								1.5		
Soluble inorganic, inhalable								0.1		
Insoluble inorganic, inhalable								0.2		
Selenium‡			0.0158	0.2		0.2		0.2	0.1	
Silver‡			0.00368*	0.01		0.01		0.1	0.01	0.03
Soluble compounds								0.01		
Thallium									0.02	
Tin, inorganic‡		1.05		2		2		2	2	
Tin Oxide		0.00105	0.00105	2		15		2	2	
Tin, Organic				0.1		0.1		0.1	0.1	0.2
Vanadium, oxide, respirable dust‡		0.00403			0.05	0.5		0.05	0.05	
Vanadium fume					0.05	0.1		0.05		
elemental				1	3					
Zinc, total dust‡		0.263	0.263	5		15				
Zinc oxide fume, respirable				5	10	5		2	2	10

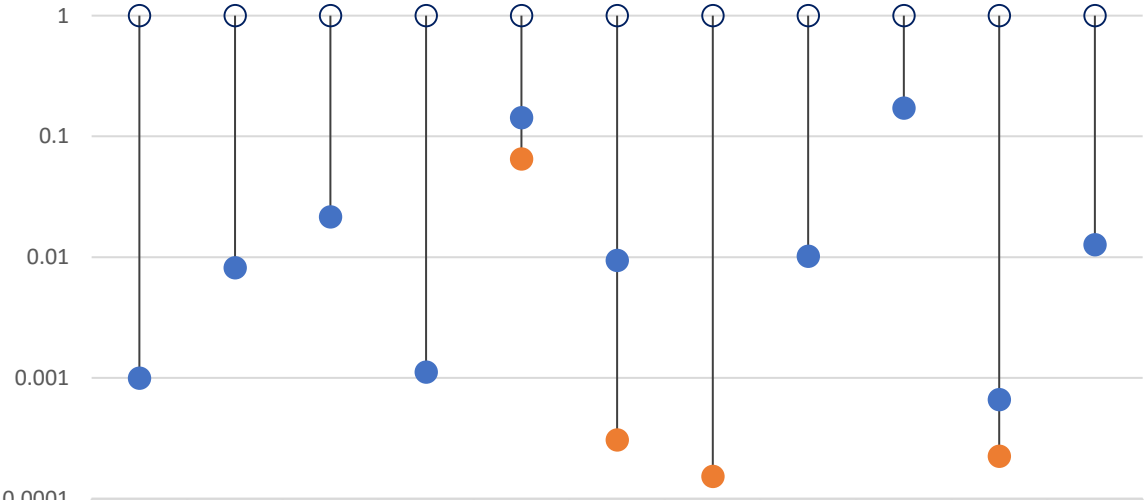
*Values from EPA: extrapolated RtR limits derived from RfD; ‡Direct respiratory toxicity; [a] TWA REL based on 10-hr, STEL based on 15-min exposure; [b] TWA PEL based on 8-hr, peak PEL based on 30-min exposure; [c] TLV TWA based on 8-hr exposure; [d] TWA REL based on 8-hr, STEL based on 15-min exposure

Figure 5. 24-hour Ambient Air Quality Guideline Values Normalized to Extrapolated Acute RtR limits



	As	B	Cu
RtR limits	1.0	1.0	1.0
Ontario AAC	0.00577	0.198	3.40
Texas AMCC	0.191		0.680

Figure 6. Annual Ambient Air Quality Guideline Values Normalized to Extrapolated Chronic RtR limits



	Al	Sb	As	Ba	Cd	Cr(VI), particulate	Cr(VI), aerosol	Mn, respirable	Mo	Ni	Se
RtR limits	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0
Ontario AAC					0.0649	0.000307	0.000153			0.000224	
Texas AMCC	0.000998	0.00816	0.0215	0.00112	0.143	0.00942		0.0102	0.171	0.000662	0.0127

Discussions

Main findings

When the oral-to-inhalation extrapolated RtR limits are compared to inhalation exposure limits based on route-specific studies available on ATSDR or EPA, the extrapolation results in an underestimation of toxicity, even when the bioavailability of both oral exposure and respiratory exposure is known. The underestimation ranges from one to three orders of magnitude; it is about 2 folds for beryllium and boron and three orders of magnitude for nickel. This suggests that there are uncertainty factors which adulterate the purpose and value of extrapolation. Major uncertainties come from direct toxicity such as direct upper and lower respiratory toxicity and transfer of xenobiotics from olfactory nerve. Other factors may be diffusion or deposition factor in lungs, toxicokinetic factor regarding distribution, metabolism, and excretion, uncertainty due to conversion from animal ingestion study to human inhalation limit, and uncertainty in relation to respiratory exposure that is not present in oral exposure. These uncertainties propose concerns that reliance on RtR extrapolation alone to derive inhalation exposure limit is insufficient to protect from adverse health effects.

The RtR limits are compared to environmental guidelines for ambient air quality. When visually inspected with graphs, the guideline values generally fall below the RtR limits. When Ontario Ambient Air Criteria (AAC) and Texas Air Monitoring Comparison Values (AMCC) guideline values are normalized to the RtR limits in the same duration of exposure, the differences are one to two orders of magnitude for 24-hour exposure, and one to four orders of magnitude for annual exposure. Ambient air quality guidelines are objectives rather than regulatory limits of metal dusts concentration in ambient air; therefore, it has to be lower than level causing health

risks to vulnerable populations who may be more affected by air quality, resulting in a lot lower values than exposure limits by ATSDR or EPA.

Interestingly, it appears that there is vast inconsistency across ambient air guidelines. For instance, the 24-hour objective values for chromium (VI) particulates differ by four orders of magnitude between Ontario and Manitoba. The short-term 24-hour ambient air standards of copper dusts in Ontario and Manitoba are above RtR limits by 5 folds. Manitoba in general has higher guideline values than other ambient air guidelines. The scientific evidence reports to support how these objectives were determined were not available, but it may be necessary to revise the air quality guidelines based on rigorous scientific evidences as the guideline values are not consistent.

The oral-to-inhalation extrapolated RtR limits are also compared to occupational air quality guidelines, and occupational guideline values are mostly above the RtR limits. This is worrisome as RtR extrapolation poses a possibility of underestimation of toxicity as discussed above. Consequently, the occupational guidelines may be exceedingly higher than the actual MRL, if the guidelines are based on RtR extrapolation alone. For some metals such as manganese, the difference between RtR limits and guidelines values are more than two orders of magnitude. This suggests that occupational air quality guidelines may need reassessment of regulatory limits, as the approach with RtR extrapolation alone is found inadequate to exclude uncertainties due to unexpected health risks or direct toxicity. The differences range from one to three orders of magnitude; therefore, the least conservative approach should include an uncertainty factor of at least 10.

limitations

The major limitation of this study is insufficient toxicokinetic data. RtR extrapolation is greatly influenced by the presence of direct toxicity, which is why the *Guidelines on Route-To-Route Extrapolation of Toxicity Data* (Interdepartmental Group on Health Risks from Chemicals, 2005) clearly state a prerequisite of no direct toxicity in the criteria. However, there are not enough toxicological data for direct upper and lower toxicity information and olfactory transfer information, bringing issues of the integrity of extrapolation. Lack of sufficient data on duration-specific exposure toxicity hinders meaningful evaluation of guidelines as well. Moreover, metabolisms for inhalation exposure and children are largely unknown; therefore, it was not considered in the extrapolation calculation for this assessment.

Bioavailability data for oral exposure is usually available from ATSDR, but inhalation bioavailability is usually not stated due to lack of scientific evidences. Therefore, I had to make an assumption of 100% respiratory bioavailability for more than half of the metals that were assessed in order to be conservative. However, it should be noted that the respiratory absorption is a lot lower than oral absorption due to low deposition rate in lungs. Depending on the ratio of bioavailability used for extrapolation, the appropriateness of the guidelines may be interpreted differently. Even when both oral bioavailability and inhalation bioavailability are available, it is often provided as a range which sometimes is very broad. For instance, the oral bioavailability of cobalt is from 18 to 97% depending on the presence of other minerals. Mercury, on the other hand, has very low oral bioavailability, but bioavailability via inhalation is 70 to 80%.

In addition, the interaction between absorbed heavy metals should be considered. The extrapolation is based on single-toxic exposure, which disregards any physiological toxicokinetic interaction with other substances. However, single-toxic exposure is rare in reality. Exposure to multiple toxics may result in a synergistic or antagonistic effect, or even potentiation.

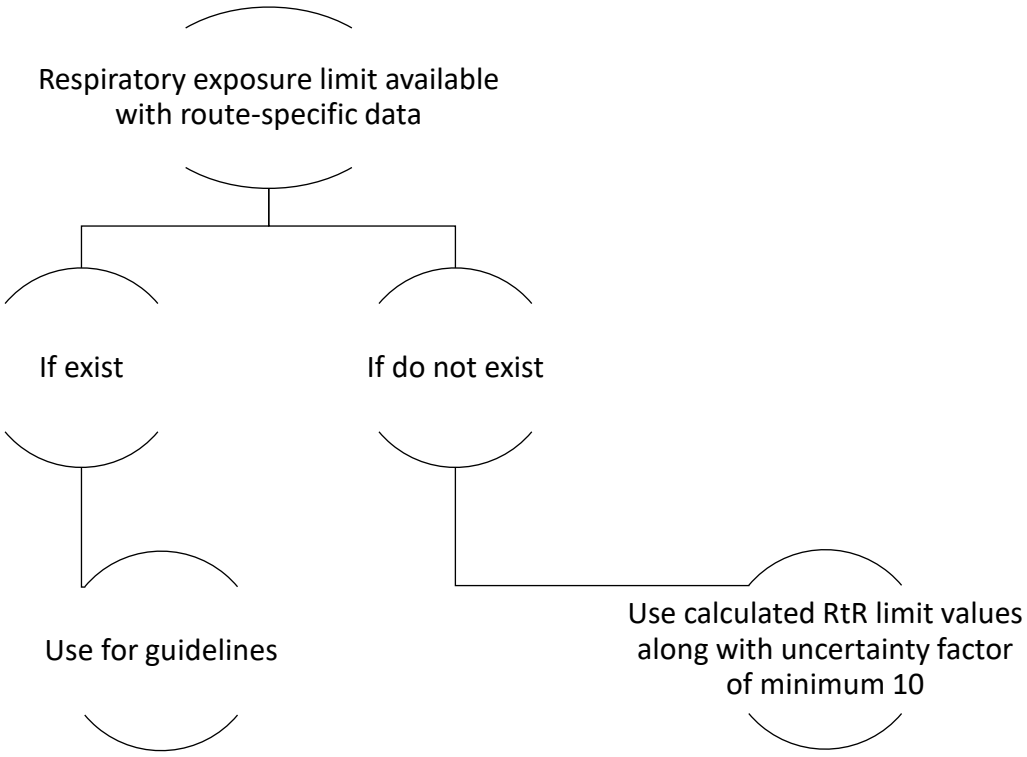
Finally, the availability of database is problematic. There is no federally managed Canadian toxicity database as ATSDR or EPA IRIS, which means that the toxicity data is heavily relied on the US databases. The only toxicity databases available from Health Canada are for human health risk assessments of federal contaminated sites and pesticides, which is not as adequate and complete like ATSDR or EPA IRIS to use for RtR extrapolation for heavy metal dusts in air.

Implications and Recommendations for Public Health Practice

The following is recommended based on the study findings:

- Measurement and component analysis of air particulates is needed to understand the main source of pollutants and implement appropriate regulations for upstream risk management.
- Further route-specific studies are warranted with various durations of exposure research for more extensive toxicity database.
- Case-specific adjustment for RtR extrapolation factors should be quantified and analyzed until sufficient data is available for generalizable adjustment. It is advised to adopt conservative extrapolation factors to be precautious.
- It is recommended to communicate with health authorities highlighting the caution regarding the approach of using RtR alone. When route-specific toxicity data is available,

it should be used for guideline values. In the absence of route-specific data, it is recommended to use at least one order of magnitude of uncertainty factor with RtR limit values to be conservative in order to protect vulnerable populations as well as to take potential direct toxicity into consideration. Relying on RtR extrapolation alone is neither sufficient nor adequate.



- Occupational air quality guidelines may need reassessment of regulatory limits as they are higher than RtR limits.
- It appears to be necessary to establish Canadian federal toxicological database for health risks with respective durations of exposure. A joint project agency with the US may be possible like the European Chemicals Agency for European countries.

Reflection of Public Health Practitioner's Role

This project emphasizes the importance of public health practitioner's role in risk assessments using appropriate extrapolation methods and evaluation of conventionally performed RtR extrapolation for air quality guidelines. Air quality guidelines should be periodically updated to comprehensively protect the health of populations with sound knowledge and familiarity with toxicology. It is reasonable that conventional RtR extrapolation could be used to establish guideline criteria for practical issues; however, the findings of this project urge that constant efforts are required to expand and update the database for inhalation-specific exposures to better address air quality objectives.

References

Agency for Toxic Substances and Disease Registry. (n.d.). ATSDR Toxic Substances Portal. Retrieved March 26, 2017, from https://www.atsdr.cdc.gov/substances/index.asp

Agency for Toxic Substances and Disease Registry. (2005). Appendix G: Calculating Exposure Doses. Retrieved February 23, 2017, from https://www.atsdr.cdc.gov/hac/phamanual/appg.html

Arts, J. H. E., Muijser, H., Appel, M. J., Kuper, C. F., Bessems, J. G. M., & Woutersen, R. A. (2004). Subacute (28-day) toxicity of furfural in Fischer 344 rats : a comparison of the oral and inhalation route. *Food and Chemical Toxicology*, *42*, 1389–1399. https://doi.org/10.1016/j.fct.2004.03.014

Association Advancing Occupational and Environmental Health. (n.d.). ACGIH - Association Advancing Occupational and Environmental Health. Retrieved March 26, 2017, from http://www.acgih.org/

Bessems, J. G. M., & Geraets, L. (2013). Proper knowledge on toxicokinetics improves human hazard testing and subsequent health risk characterisation . A case study approach. *Regulatory Toxicology and Pharmacology*, *67*, 325–334. https://doi.org/10.1016/j.yrtph.2013.08.010

Borghoff, S. J., Parkinson, H., & Leavens, T. L. (2010). Physiologically based pharmacokinetic rat model for methyl tertiary -butyl ether ; comparison of selected dose metrics following various MTBE exposure scenarios used for toxicity and carcinogenicity evaluation. *Toxicology*, *275*(1–3), 79–91. https://doi.org/10.1016/j.tox.2010.06.003

British Columbia Ministry of Environment. (2016). *British Columbia Ambient Air Quality Objectives*.

Caravanos, J., Weiss, A. L., Blaise, M. J., & Jaeger, R. J. (2006). A survey of spatially distributed exterior dust lead loadings in New York City. *Environmental Research*, *100*(2), 165–172. https://doi.org/10.1016/j.envres.2005.05.001

Cheng, X., Huang, Y., Long, Z., Ni, S., Shi, Z., & Zhang, C. (2017). Characteristics, Sources and Health Risk Assessment of Trace Metals in PM10 in Panzhihua, China. *Bulletin of Environmental Contamination and Toxicology*, *98*(1), 76–83. https://doi.org/10.1007/s00128-016-1979-0

Chiu, W. A., & White, P. (2006). Steady-State Solutions to PBPK Models and Their Applications to Risk Assessment I : Route-to-Route Extrapolation of Volatile Chemicals. *Risk Analysis*, *26*(3), 769–780. https://doi.org/10.1111/j.1539-6924.2006.00762.x

Clewell, H. J., Gentry, P. R., Gearhart, J. M., Covington, T. R., Banton, M. I., & Andersen, M. E. (2001). Development of a Physiologically Based Pharmacokinetic Model of Isopropanol and Its Metabolite Acetone. *Toxicological Sciences*, *172*, 160–172.

Department for Environment Food and Rural Affairs. (2012). *National Air Quality Objectives*.

Environment Canada. (2013). Canadian National Ambient Air Quality Objectives : Process and Status, (Appendix 1), 1–8.

Estarlich, M., Ballester, F., Davdand, P., Llop, S., Esplugues, A., Fernández-Somoano, A., … Iñiguez, C. (2016). Exposure to ambient air pollution during pregnancy and preterm birth: A Spanish multicenter birth cohort study. *Environmental Research*, *147*, 50–58. https://doi.org/10.1016/j.envres.2016.01.037

Falk-filipsson, A., Hanberg, A., Victorin, K., Warholm, M., & Walle, M. (2007). Assessment factors — Applications in health risk assessment of chemicals. *Environmental Research*, *104*, 108–127. https://doi.org/10.1016/j.envres.2006.10.004

Flynn, M. R., & Susi, P. (2009). Neurological risks associated with manganese exposure from welding operations – A literature review. *International Journal of Hygiene and Environmental Health*, *212*(5), 459–469. https://doi.org/10.1016/j.ijheh.2008.12.003

Franklin, M., Koutrakis, P., & Schwartz, P. (2008). The role of particle composition on the association between PM2.5 and mortality. *Epidemiology*, *19*(5), 680–9. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/18714438

Galarneau, E., Wang, D., Dabek-Zlotorzynska, E., Siu, M., Celo, V., Tardif, M., … Jiang, Y. (2016). Air toxics in Canada measured by the National Air Pollution Surveillance (NAPS) program and their relation to ambient air quality guidelines. *Journal of the Air & Waste Management Association*, *66*(2), 184–200. https://doi.org/10.1080/10962247.2015.1096863

Gao, P., Liu, S., Ye, W., Lin, N., Meng, P., Feng, Y., … Xing, B. (2015). Assessment on the occupational exposure of urban public bus drivers to bioaccessible trace metals through resuspended fraction of settled bus dust. *Science of The Total Environment*, *508*, 37–45. https://doi.org/10.1016/j.scitotenv.2014.11.067

Geraets, L., Bessems, J. G. M., Zeilmaker, M. J., & Bos, P. M. J. (2014). Human risk assessment of dermal and inhalation exposures to chemicals assessed by route-to-route extrapolation: The necessity of kinetic data. *Regulatory Toxicology and Pharmacology*, *70*(1), 54–64. https://doi.org/10.1016/j.yrtph.2014.05.024

Government of Alberta. (2016). *Alberta Ambient Air Quality Objectives and Guidelines Summary*. Retrieved from http://aep.alberta.ca/air/legislation/ambient-air-quality-objectives/documents/AAQO-Summary-Jun2016.pdf

Government of Manitoba. (2005). *Manitoba Ambient Air Quality Criteria* (Vol. 100).

Himmelstein, M. W., Serex, T. L., Buck, R. C., Weinberg, J. T., Mawn, M. P., & Russell, M. H. (2012). 8:2 fluorotelomer alcohol: A one-day nose-only inhalation toxicokinetic study in the Sprague-Dawley rat with application to risk assessment. *Toxicology*, *291*, 122–132. https://doi.org/10.1016/j.tox.2011.11.005

Hinderliter, P. M., Delorme, M. P., & Kennedy, G. L. (2006). Perfluorooctanoic acid : Relationship between repeated inhalation exposures and plasma PFOA concentration in the rat.

Toxicology, *222*, 80–85. https://doi.org/10.1016/j.tox.2006.01.029

Interdepartmental Group on Health Risks from Chemicals. (2005). *Guidelines on route-to-route extrapolation of toxicity data when assessing health risks of chemicals Draft v6.0*. Retrieved from http://ieh.cranfield.ac.uk/ighrc/cr12[1].pdf

Järup, L. (2003). Hazards of heavy metal contamination. *British Medical Bulletin*, *68*, 167–82. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/14757716

Jayawardana, P. L. (2004). Non-specific occupational health conditions among brass workers at Gadaladeniya, Sri Lanka. *The Ceylon Medical Journal*, *49*(4), 122–7. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/15693451

Kong, S., Lu, B., Ji, Y., Zhao, X., Bai, Z., Xu, Y., … Jiang, H. (2012). Risk assessment of heavy metals in road and soil dusts within PM2.5, PM10 and PM100 fractions in Dongying city, Shandong Province, China. *Journal of Environmental Monitoring*, *14*(3), 791. https://doi.org/10.1039/c1em10555h

Lacasaña, M., Esplugues, A., & Ballester, F. (2005). Exposure to ambient air pollution and prenatal and early childhood health effects. *European Journal of Epidemiology*, *20*(2), 183–99. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/15792286

Laurent, O., Hu, J., Li, L., Kleeman, M. J., Bartell, S. M., Cockburn, M., … Wu, J. (2016). Low birth weight and air pollution in California: Which sources and components drive the risk? *Environment International*, *92–93*, 471–477. https://doi.org/10.1016/j.envint.2016.04.034

Lavigne, É., Bélair, M., Do, M. T., Stieb, D. M., Hystad, P., Donkelaar, A. Van, … Walker, M. (2017). Maternal exposure to ambient air pollution and risk of early childhood cancers : A population-based study in Ontario , Canada. *Environment International*, *100*(2), 139–147. https://doi.org/10.1016/j.envint.2017.01.004

Liang, Z., Wu, L., Fan, L., & Zhao, Q. (2014). Ambient air pollution and birth defects in Haikou city, Hainan province. *BMC Pediatrics*, *14*(1), 283. https://doi.org/10.1186/s12887-014-0283-6

Lippmann, M. (2010). Targeting the components most responsible for airborne particulate matter health risks. *Journal of Exposure Science & Environmental Epidemiology*, *20*(2), 117–8. https://doi.org/10.1038/jes.2010.1

Lippmann, M. (2012). Particulate matter (PM) air pollution and health: regulatory and policy implications. *Air Quality, Atmosphere & Health*, *5*(2), 237–241. https://doi.org/10.1007/s11869-011-0136-5

Lippmann, M., & Chen, L.-C. (2009). *Health effects of concentrated ambient air particulate matter (CAPs) and its components*. *Critical reviews in toxicology* (Vol. 39). https://doi.org/10.3109/10408440903300080

Liu, S., Krewski, D., Shi, Y., Chen, Y. U. E., & Burnett, R. T. (2007). Association between maternal exposure to ambient air pollutants during pregnancy and fetal growth restriction. *Journal*

of Exposure Science and Environmental Epidemiology, *17*, 426–432. https://doi.org/10.1038/sj.jes.7500503

Liu, Y., Yan, S., Poh, K., Liu, S., Iyioriobhe, E., & Sterling, D. A. (2016). Impact of air quality guidelines on COPD sufferers. *International Journal of Chronic Obstructive Pulmonary Disease*, *11*(1), 839–72. https://doi.org/10.2147/COPD.S49378

Lorber, M., Gibb, H., Grant, L., Pinto, J., Pleil, J., & Cleverly, D. (2007). Assessment of Inhalation Exposures and Potential Health Risks to the General Population that Resulted from the Collapse of the World Trade Center Towers. *Risk Analysis*, *27*(5), 1203–1221. https://doi.org/10.1111/j.1539-6924.2007.00956.x

Malley, C. S., Kuylenstierna, J. C. I., Vallack, H. W., Henze, D. K., Blencowe, H., & Ashmore, M. R. (2017). Preterm birth associated with maternal fine particulate matter exposure: A global, regional and national assessment. *Environment International*, *101*, 173–182. https://doi.org/10.1016/j.envint.2017.01.023

Mendola, P., Wallace, M., Hwang, B. S., Liu, D., Robledo, C., Männistö, T., … Grantz, K. L. (2016). Preterm birth and air pollution: Critical windows of exposure for women with asthma. *Journal of Allergy and Clinical Immunology*, *138*(2), 432–440.e5. https://doi.org/10.1016/j.jaci.2015.12.1309

Min, J., & Min, K. (2017). Exposure to ambient PM10 and NO2 and the incidence of attention-deficit hyperactivity disorder in childhood. *Environment International*, *99*, 221–227. https://doi.org/10.1016/j.envint.2016.11.022

Ministère du Développement durable, & de l'Environnement et de la Lutte contre les changements climatiques. (2016). Normes et critères québécois de qualité de l'atmosphère, version 5. Retrieved from http://www.mddelcc.gouv.qc.ca/air/criteres/Normes-criteres-qc-qualite-atmosphere.pdf

National Institute for Occupational Safety and Health. (n.d.). CDC - The National Institute for Occupational Safety and Health (NIOSH). Retrieved March 26, 2017, from https://www.cdc.gov/niosh/

Naumann, B. D., Weideman, P. A., Sarangapani, R., Hu, S., Dixit, R., & Sargent, E. V. (2009). Investigations of the Use of Bioavailability Data to Adjust Occupational Exposure Limits for Active Pharmaceutical Ingredients. *Toxicological Sciences*, *112*(1), 196–210. https://doi.org/10.1093/toxsci/kfp195

Nduka, J. K., Onyenezi Amuka, J. P., Onwuka, J. C., Udowelle, N. A., & Orisakwe, O. E. (2016). Human health risk assessment of lead, manganese and copper from scrapped car paint dust from automobile workshops in Nigeria. *Environmental Science and Pollution Research*, *23*(20), 20341–20349. https://doi.org/10.1007/s11356-016-7219-7

Newfoundland and Labrador. (2004). Regulation 39/04, Air Pollution Control Regulations, 2004 under the Environmental Protection Act (O.C. 2004-232).

Noh, J., Sohn, J., Cho, J., Cho, S.-K., Choi, Y. J., Kim, C., & Shin, D. C. (2016). Short-term Effects of

Ambient Air Pollution on Emergency Department Visits for Asthma: An Assessment of Effect Modification by Prior Allergic Disease History. *Journal of Preventive Medicine and Public Health*, *49*(5), 329–341. https://doi.org/10.3961/jpmph.16.038

Ontario Ministry of the Environment. (2012). *Ontario's Ambient Air Quality Criteria*.

Park, R. M., Bena, J. F., Stayner, L. T., Smith, R. J., Gibb, H. J., & Lees, P. S. J. (2004). Hexavalent Chromium and Lung Cancer in the Chromate Industry: A Quantitative Risk Assessment. *Risk Analysis*, *24*(5), 1099–1108. https://doi.org/10.1111/j.0272-4332.2004.00512.x

Pauluhn, J. (2003). Issues of dosimetry in inhalation toxicity. *Toxicology Letters*, *140–141*, 229–238. https://doi.org/10.1016/S0378-4274(03)00077-8

Pedersen, C. B., Raaschou-Nielsen, O., Hertel, O., & Mortensen, P. B. (2004). New Directions: Air pollution from traffic and schizophrenia risk. *Atmospheric Environment*. https://doi.org/10.1016/j.atmosenv.2004.04.011

Pepelko, W. E., & Withey, J. R. (1985). Methods for route-to-route extrapolation of dose. *Toxicology and Industrial Health*, *1*(4), 153–175.

Quincey, P., & Butterfield, D. (2009). Ambient air particulate matter PM10 and PM2.5: developments in European measurement methods and legislation. *Biomarkers*, *14*, 34–38. https://doi.org/10.1080/13547500902965484

Rennen, M. A. ., Bouwman, T., Wilschut, A., Bessems, J. G. ., & Heer, C. De. (2004). Oral-to-inhalation route extrapolation in occupational health risk assessment: a critical assessment. *Regulatory Toxicology and Pharmacology*, *39*(1), 5–11. https://doi.org/10.1016/j.yrtph.2003.09.003

Schröder, K., Escher, S. E., Hoffmann-Dörr, S., Kühne, R., Simetska, N., & Mangelsdorf, I. (2016). Evaluation of route-to-route extrapolation factors based on assessment of repeated dose toxicity studies compiled in the database RepDose. *Toxicology Letters*, *261*, 32–40. https://doi.org/10.1016/j.toxlet.2016.08.013

Semple, S. (2005). Assessing occupational and environmental exposure. *Occupational Medicine (Oxford, England)*, *55*(6), 419–24. https://doi.org/10.1093/occmed/kqi135

Shankaran, H., Adeshina, F., & Teeguarden, J. G. (2013). Physiologically-based pharmacokinetic model for Fentanyl in support of the development of Provisional Advisory Levels. *Toxicology and Applied Pharmacology*, *273*(3), 464–476. https://doi.org/10.1016/j.taap.2013.05.024

Siddique, S., & Banerjee, M. (2011). Attention-deficit hyperactivity disorder in children chronically exposed to high level of vehicular pollution. *European Journal of Pediatrics*, *170*, 923–929. https://doi.org/10.1007/s00431-010-1379-0

Singh, D. K., & Gupta, T. (2016). Source apportionment and risk assessment of PM1 bound trace metals collected during foggy and non-foggy episodes at a representative site in the Indo-Gangetic plain. *Science of The Total Environment*, *550*, 80–94.

https://doi.org/10.1016/j.scitotenv.2016.01.037

Srám, R. J., Binková, B., Dejmek, J., & Bobak, M. (2005). Ambient air pollution and pregnancy outcomes: a review of the literature. *Environmental Health Perspectives*, *113*(4), 375–82. https://doi.org/10.1289/ehp.6362

Sweeney, L. M., & Gargas, M. L. (2016). Route-to-route extrapolation of 1 ,2-dichloroethane studies from the oral route to inhalation using physiologically based pharmacokinetic models. *Regulatory Toxicology and Pharmacology*, *81*, 468–479. https://doi.org/10.1016/j.yrtph.2016.10.005

Sweeney, L. M., Saghir, S. A., & Gargas, M. L. (2008). Physiologically based pharmacokinetic model development and simulations for ethylene dichloride (1 , 2-dichloroethane) in rats. *Regulatory Toxicology and Pharmacology*, *51*, 311–323. https://doi.org/10.1016/j.yrtph.2008.05.002

Tan, J.-H., Duan, J.-C., Ma, Y.-L., Yang, F.-M., Cheng, Y., He, K.-B., … Wang, J.-W. (2014). Source of atmospheric heavy metals in winter in Foshan, China. *Science of The Total Environment*, *493*, 262–270. https://doi.org/10.1016/j.scitotenv.2014.05.147

Texas Commission on Environmental Quality. (2016). *Air Monitoring Comparison Values (AMCVs)*.

United States Department of Labor. (n.d.). Occupational Safety and Health Administration. Retrieved March 26, 2017, from https://www.osha.gov/

US Environmental Protection Agency. (n.d.). Integrated Risk Information System. Retrieved March 26, 2017, from https://www.epa.gov/iris

US Environmental Protection Agency. (2008). National Ambient Air Quality Standards Table. Retrieved February 27, 2017, from https://www.epa.gov/criteria-air-pollutants/naaqs-table

Worksafe BC. (2015). Table of exposure limits for chemical and biological substances, (L), 1–19. Retrieved from http://www2.worksafebc.com/PDFs/regulation/ExposureLimits.pdf?_ga=1.164024185.732066339.1446186338

World Health Organization. (2006). WHO Air quality guidelines for particulate matter, ozone, nitrogen dioxide and sulfur dioxide - Global update 2005 - Summary of risk assessment. *Geneva: World Health Organization*, 1–22. https://doi.org/10.1016/0004-6981(88)90109-6

World Health Organization. (2016a). Ambient (outdoor) air quality and health. Retrieved February 23, 2017, from http://www.who.int/mediacentre/factsheets/fs313/en/

World Health Organization. (2016b). WHO Global Urban Ambient Air Pollution Database (update 2016). Retrieved February 23, 2017, from http://who.int/phe/health_topics/outdoorair/databases/cities/en/

World Health Organization. (2017a). *Atlas on children's health and the environment*. Geneva.

Retrieved from http://apps.who.int/iris/bitstream/10665/254677/1/9789241511773-eng.pdf?ua=1

World Health Organization. (2017b). *Don't pollute my future! The impact of the environment on children's health*. Geneva. Retrieved from http://apps.who.int/iris/bitstream/10665/254678/1/WHO-FWC-IHE-17.01-eng.pdf?ua=1

Yao, C., Chen, Y., Zhu, X., Liu, Y., Zhang, J., Hou, L., … Cao, J. (2016). Air Pollution and the Risk of Birth Defects in Anqing City, China. *Journal of Occupational and Environmental Medicine*, *58*(4), e124–e127. https://doi.org/10.1097/JOM.0000000000000676

Zereini, F., Wiseman, C., Alt, F., Messerschmidt, J., Müller, J., & Urban, H. (2001). Platinum and rhodium concentrations in airborne particulate matter in Germany from 1988 to 1998. *Environmental Science & Technology*, *35*(10), 1996–2000. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/11393979