EDITORIAL

Chemical Risk without Concurrent External Exposure!

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Chemicals are health hazards, under specific sets of conditions transforming into a potential "risk". In the story of creation and the Garden of Eden, a poisonous fruit was a hazard, but malicious intervention of the serpent convincing Eve and Adam to eat the poisonous fruit was the risk. A very simple model is: **Hazard → Exposure → Risk**

In recent decades, regulatory measures that limit exposures to harmful chemicals have protected the population from the risks of chemicals. Use of leaded gas, for example, was banned beginning in the 1970's leading to a drastic decrease in the risk of exposure at the population level. It is generally accepted that when there is no exposure, exposure is below the regulatory limits or if we are not aware of toxic exposures, risks related to contacts to chemicals are negligible.

This editorial addresses the potential health risks of chemicals when exposure is considered to be negligible *(di minimums)* or nonexistent. For this argument, we assumed a reference population such as Canadian residents that are assumed to not be exposed at levels over the regulatory limits of chemicals, and we discuss the exclusions. In none of these scenarios is medical treatment proposed.

Indefinite risk of unknown or mixed exposures

There is convincing evidence regarding recognised harmful chemicals; however, there are over 100,000 registered chemicals, for many of which the toxicity has not been studied or only studied for selected potential outcomes. In the current regulatory framework, c*hemicals are generally considered to be innocent until proven guilty!* In addition, the risks associated with the interactions between chemicals remain largely unstudied. Under these conditions, our reference population might not be as protected as we hope.

Regulatory failures

Despite the regulatory standards in place, the numbers of foods, mediations and consumer products recalled on a daily basis show the extent of regulatory failures. In 2007, an outbreak of acute selenium toxicity as a result of a mislabeled liquid dietary supplement that contained 200 times the labeled concentration led to the identification of 201 cases in 10 states and one hospitalization. Diarrhea (78%), fatigue (75%), hair loss (72%) and joint pain were common symptoms ([1]).

Commercial foods such as fish and shellfish are subject to regulation to ensure safe levels of marine biotoxins such as Saxitoxin; However, subgroups that consume large quantities of these foods, such as self-harvesters among First Nations and coastal residents as well as recreational fishermen, might exceed the recommended intake of biotoxins and thereby increase their risk of adverse health outcomes.[2]

Skewed exposure in certain communities

Regulatory limits typically incorporate uncertainty factors for inter-species differences and inter-individual variability in vulnerability, providing a conservative margin of safety. Nevertheless, it is important to consider particularly vulnerable subpopulations, such as those for whom diet differs from that of the general population, creating different risk profiles.

Under-appreciated risk of long-term low dose exposures

Recent studies of endocrine-disrupting chemicals have challenged traditional concepts in toxicology, most notably the doctrine of "the dose makes the poison." Some chemicals have effects at low doses that are not predicted by the effects at higher doses, so called "chemicals with non-monotonic dose-response curves" ([3]). In addition, it is known that certain chemicals cause harm at levels below regulatory limits ([4]). For example, despite substantial reductions in population exposures to lead due to policies such as the elimination of leaded gas, very low dose lead exposures that remain still affect intellectual abilities in children ([5]).

Evidence that chemical exposure through certain media, such as manganese in drinking water ([6]), and from particular pathways, including cadmium uptake from the nasal mucosa or olfactory nerve pathways into the peripheral and central neurons with an increase in blood brain barrier permeability, is abundant ([7]).

Familial exposure

Occupational exposures to chemicals are well recognised and regulated. However, families of workers may suffer second-hand exposure from contaminated clothes, placing them at greater risk than the general population. Pregnant women and children are especially sensitive subgroups in this scenario

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Vicinity exposure

People who are living in the vicinity of industrial establishments, such as families of workers in remote mining settings, are at higher risk of exposure than the general population.

While dry cleaners that use highly toxic tetrachloroethylene and trichloroethylene are regulated as occupational exposures for healthy adults that work for 8 hours per day, families that live above dry cleaners and are exposed for extended periods of time (i.e. 24 hours a day) are not covered by current regulations and yet might be at higher risk. People who reside near crematoriums are at higher risk of exposure to mercury that is emitted from cremation of dental amalgam.

Traveller's exposure

While it has been taken for granted that exposure to lead via air is limited among Canadians, individuals who travel internationally to highly air polluted cities are exposed during their stay; this is even more important for frequent and long-term travellers. In addition, travellers often self-import foods originated from other countries that might not be subject to strict regulations.

Under-recognised sources of exposure

Certain populations use tainted folk and traditional medicines ([8]) and street drugs ([9]) that are occasionally prepared or produced with highly toxic elements such as lead.

Long term congenital (hidden internal) exposure

Blood half-lives (HL) of certain chemicals, such as cadmium ([10]), are very long (sometimes years). For certain chemicals that have shorter blood HL, other compartments can store and gradually release it, contributing to internal dose. For example, although it is widely recognised that blood lead HL is around 30 days according to tracer studies, lead has a much longer HL in bone, which acts as a source of internal exposure ([11]). Lead kinetics in the human body follow a three [four] complement model with lead stored in bones (and in particular deep bones) ([12 13]) for years.

This fact has clinical implications for individuals who emigrate from countries with high exposures to countries with lower exposures. Fetuses of newcomers who get pregnant years after immigrating can be at higher risk of exposure to cadmium and lead as compared to the general population. Bone stores may pose a threat to women of reproductive age long after exposure has declined ([14]).

Source mobilisation exposure

Calcium metabolism changes drastically in humans during pregnancy and lactation, and in turn bone lead is mobilized and transferred to the more bioavailable compartment of the maternal circulation, increasing the risk of toxic effects to both the fetus and the mother ([11 15]). It is important to note that lead is mobilized from bone during the latter half of pregnancy. Increased calcium intake may reduce bone demineralization and hence lead mobilization ([16]). Immobilization and vitamin D deficiency also mobilise calcium from bones and, in turn, stored lead (Figure 1).

--- Weight loss; certain chemicals such as dioxins, are stored in fat tissue. Any changes in fat mobilisation, such as weight loss, may increase blood levels, with additional internal risks.

Discontinued exposure, but delayed effects

Lifetime and perhaps even shorter periods of exposure to toxic elements increases cumulative cancer risk. Exposure leads to clinical manifestation, but also induces sub-clinical and molecular changes at earlier stages with no obvious clinical findings. Some individuals exposed to toxic chemicals in the past might show clinical findings only after a latency period, or so called "delayed effects". It has been shown that the rates of new health complications such as cancer and nonspecific secondary effects increase decades after exposure to chemical warfare agents ([17 18]). Newcomers to Canada who were exposed in the past to aflatoxin in foods may be at increased risk of hepatocellular carcinoma long after immigration. Higher past exposure to cadmium, with its long HL, is associated with a delayed increase in the risk of kidney diseases.

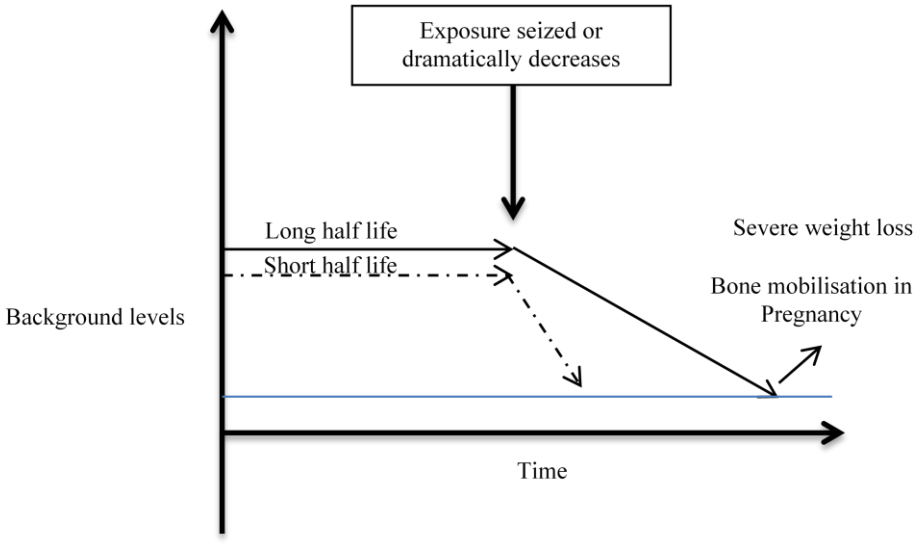

Figure 1. Risk related to toxic exposure, when current contact with toxic hazard does not exist (hypothetical model).

Transgenerational delayed effects in unexposed generations

Research has established that toxicants can transfer from pregnant women to fetuses through umbilical cord. As a result, fetuses before being born are exposed to chemicals. Recent studies has revealed one step further; --- Reproductive cells of the fetus (third generation) can also be affected ([19]). Zebrafish studies suggested that short-term exposures to some chemicals during pregnancy can cause reproductive system damage, hormonal changes, alter body weight, and even increase the risk of cancer for great-grandchildren of exposed animals ([20] [21]). In fact, we are what our grandmothers ate (exposed to) long before our life began! Gene function alteration due to chemical exposure (epigenetics) can be passed on not only to the immediate offspring, but also to grandchildren and perhaps even great-grandchildren ([22])!

Age, bioaccumulation and higher rate of exposure

Consuming one liver or one kidney of an "old" sea lion (traditional food among First Nations) might result in vitamin A and cadmium intakes that exceed the daily allowable intakes for a 2 year old child (under published calculation).

Even at stable background exposure levels, chemicals such as lead and cadmium bio-accumulate as individuals age ([23-25]). Therefore, older people are at higher risk even if their current exposure is similar to the rest of population.

newcomers as compared to their peers, these minor routes of chemical detoxification become less effective and increase internal exposure.

Less effectiveness of health messaging for new comers

The appropriate safe limits for setting the regulatory values are scientifically, intellectually and practically designed. Recommendations provided by Health Canada (2007)[27] regarding mercury exposure from seafood, for example took into account sensitive populations and variations among fish species in mercury concentrations. Newcomers speaking languages other than English might not be able to access these messages compared to the general public, leading to higher relative rates of fish consumption, with increased risk of mercury exposure in

CONCLUSION

In this editorial we proposed a series of scenarios in which chemical-related risks exist in the absence of current exposure to the chemical of interest or when exposure does not exceed regulation limits. These considerations have greater clinical implications for newcomers from highly polluted geographical areas. --- It is time to update the

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