APPENDIX R: SUMMARY OF RECENT SCIENTIFIC LITERATURE AND POLICY ON BLOOD LEAD LEVELS

In light of an increasing body of scientific research demonstrating a broad spectrum of health outcomes associated with lead exposure, most notably neurological effects among children at low blood lead levels (*i.e.*, less than 10 µg/dL), various regulatory agencies have, or are in the midst of, updating their respective health-based policies and guidelines concerning lead.

Of the authoritative resources available, most agree that BLLs < 10 µg/dL in children and adults are associated with a broad range of health-related outcomes including cardiovascular effects; renal effects; developmental/reproductive effects; nervous system effects; and immune system related effects. There is general agreement that a wide spectrum of neurological effects (*e.g.,* decreased cognitive function, behavior effects, impulsivity, inattention, and memory effects, *etc.*) in children occur at BLLs < 10 µg/dL and in some cases < 2 µg/dL. Many of the agencies (US EPA, 2006; ATSDR, 2007; HC, 2013a,b; US EPA, 2012) make reference to the pooled analysis conducted by Lanphear *et al*. (2005) as some of the most compelling evidence to support the nonlinear nature of the dose-response relationship between low BLLs and cognitive function and thus the lack of an effects-based threshold.

Health Canada has published a report in February of 2013, entitled “Final Human Health State of the Science Report on Lead” (HC, 2013a) in response to this increasing body of scientific evidence demonstrating health effects occurring below the current Canadian blood lead intervention level (10 µg/dL). The State of the Science Report (HC, 2013a) is not a comprehensive or critical review of all available scientific data but rather a summary of information used to form the basis of the evaluation. The health effects assessment presented by HC (2013a) focused on chronic health effects in humans where sufficient evidence was present that either developmental neurotoxic, neurodegenerative, cardiovascular, renal, or reproductive effects are occurring below the current Canadian intervention level of 10 µg/dL. HC (2013a) provided an overarching discussion of the key scientific studies and summarized (in tabular form) the effects observed and their corresponding BLL for each study under the five (5) endpoints mentioned above.

Health Canada (HC, 2013a) concluded that there is evidence of health effects occurring below 10 µg/dL, in fact, HC (2013a) states that there is sufficient evidence that BLLs below 5 µg/dL are associated with adverse health effects and that developmental neurotoxicity (the endpoint associated with the lowest BLL in both observational studies and *in vivo* experiments) can occur at BLLs as low as 1 to 2 µg/dL. Developmental neurotoxic effects have been demonstrated to persist in humans into the late teen-age years while in animals, these effects have been shown to persist after exposure has ended and lead concentrations in both blood and brain have returned to control levels. According to HC (2013a), the majority of data collected from observational studies does not point to a population-based threshold (below which developmental neurotoxicity is not expected to occur) within the range of current environmental exposures.

HC (2013a) indicated that the relationship between IQ score (in children) and BLLs is the strongest line of evidence of adverse effects in humans below a BLL of 10 µg/dL and that neurodevelopmental effects among infants and children is the primary health effect of concern, with IQ score being the most sensitive of all neurological related endpoints. Health Canada (2013a) considers the meta analysis conducted by Lanphear *et al*. (2005) as the most comprehensive analysis concerning developmental neurotoxicity and is of the mind that selecting children as the most susceptible subpopulation and neurodevelopmental effects as the

most critical endpoint is protective of other adverse effects of lead exposure (*i.e.*, cardiovascular, renal, and reproductive effects) across the entire population.

The outcome of this State of the Science report is consistent with conclusions from other regulatory reviews. The 10 µg/dL intervention level for lead is no longer considered to be health protective, as there is no evidence of a threshold for critical lead-induced health effect. It is considered appropriate to apply a conservative approach when characterizing risk; accordingly, additional measures to further reduce exposures of lead to Canadians are warranted**.** Health Canada has also published a second report in February of 2013, entitled "Risk Management Strategy for Lead" (HC, 2013b). The objective of the Proposed Lead Risk Management Strategy was to provide continued support of the existing programs (under the Canadian federal risk management strategy for lead) and to pursue additional actions to further reduce lead exposure to the greatest extent practical (HC, 2013b). Blood lead levels of Canadians have declined significantly over the past 30 years. That said, in response to the evidence that health effects are occurring at levels below 10 µg/dL, and in consideration that it is appropriate to apply a conservative approach when characterizing risk, it was concluded that additional measures to further reduce exposures of Canadians to lead, with a particular focus on vulnerable populations, are warranted. Accordingly, the proposed risk management objective for lead is to pursue additional management measures to reduce exposure to lead, and hence associated risks, to the greatest extent practicable. The overall Government of Canada risk management objective is to reduce exposure to lead to the greatest extent practicable by strengthening current efforts in priority areas where the government can have the greatest impact upon exposure of Canadians.

In developing a new Canadian Soil Quality Guideline (SQG) value for lead, CCME (2012a,b) has established a reference value for lead based on the most studied neurodevelopmental toxicity endpoint, for which there is also the greatest weight of evidence, related to the adverse consequences of chronic early-life lead exposure on intelligence tests (IQ) among school-aged children. The level of protection associated with the draft SQG values relate to soil concentrations resulting in no more than a one (1) IQ point decrease on a population level, as measured by full-scale Wechsler IQ. The current literature also suggests that neonates and infants are the most sensitive receptors with respect to lead exposure and as such the selection of neonates and infants as a susceptible subpopulation and neurodevelopmental effects as the critical health effect was considered protective for other adverse effects of lead across the entire population (CCME, 2012b).

For adults, cardiovascular toxicity was identified as the most sensitive endpoint for lead toxicity. The current epidemiological literature supports a "relatively mild, but statistically significant" association between whole BLLs and increases in blood pressure, particularly systolic blood pressure (SBP). CCME (2012b) notes that based on a number of published studies, each doubling of BLLs is associated with an increase in SBP of approximately 1 mm Hg. It also notes that epidemiological evidence is suggestive, but not entirely consistent, of an association between environmental lead exposure and SBP or risk of hypertension among subjects with average BLLs less than 10 µg/dL (CCME, 2012b).

The Toxicological Reference Value (TRV) used by CCME (2012b) to derive SQGs for lead was calculated using a benchmark concentration approach. The TRV for lead is referred to as a Bench Mark Concentration Lower (bound) (or BMCL) and is typically derived using studies that express observed adverse effects (among adults and children) as a function of BLLs. A BMCL typically represents the upper bound estimate of the slope of the dose response relationship. The CCME (2012b) employed the use of a loss in IQ (for children) or increase in SBP (for

adults) of 1% (on a population basis) as an adverse effect level for the purposes of deriving a provisional TRV. It is noted that the provisional TRV derived by CCME (2012b) does not represent a daily exposure rate for which a given population can experience without an unacceptable risk of adverse health effects (*i.e*., it does not represent a threshold).

The Office of Environmental Health Hazard Assessment (CalOEHHA, 2007) among other regulatory agencies, conducted dose-response analyses using the Lanphear *et al*. (2005) dataset. The CalOHHEA (2007) analysis indicated that an incremental increase of 1 µg/dL blood lead was associated with a 1% decrease in IQ score on a population basis. The CCME (2012b) employed the results of CalOEHHA (2007) analyses to represent their provisional lead TRV for infants, toddlers, children and adolescents (*i.e.,* an incremental increase of 1 µg/dL blood lead was associated with a 1% decrease in IQ score in a population basis). For adults, SBP was selected as the critical endpoint and data generated by Vupputuri *et al*. (2003) was used to evaluate a dose-response relationship. An incremental increase of 1.4 µg/dL blood lead (among Canadian adult females) was associated with a 1% increase in SPB on a population basis. This relationship was used by CCME (2012b) to derive SQG protective of the adult population.

One of the largest uncertainties is the ability to quantify health effects based on an IQ drop of 1 point. IQ tests are generally considered blunt measures of neurologic status, and the ability to accurately identify such a minute drop as correlated to neurological impacts is questionable (CCME, 2012b). For example, as noted by CCME (2012b), the World Health Organization (WHO, 2001) has indicated that IQ estimates computed from the Wechsler scales or other measures have not, in general, been demonstrated to be particularly sensitive to neurotoxic exposure. It has also been widely documented that there are a large number of confounders that must be considered when measuring an effect on children's intelligence, including socio-economic status (SES), parental IQ, and the quality of the home environment.

The CCME (2012b) indicated that pooled analysis by Lanphear *et al.* (2005), the dataset used to derive the lead TRV, included a large number of diverse subjects with a sufficient number of pre-school and school-age children with BLLs ≤10 µg/dL to provide it sufficient statistical power to describe the relationship between BLLs and cognitive function. However, there is uncertainty regarding the extrapolation of the dose-response curve to levels currently found in Canadians as the lowest BLL in the Lanphear *et al*. (2005) study was 2.4 µg/dL.

Regardless, CCME (2012b) indicates that the level of confidence in the scientific literature reporting the association between lead exposure and neurodevelopmental toxicity in humans is high. They note that numerous human observational studies that assess multiple organs or systems are available, and the critical health effects identified are based on well-established endpoints and are supported by mechanistic data as well as studies conducted in laboratory animals.

The issue of what magnitude of lead exposure, as measured by a blood lead concentration, should trigger intervention remains outstanding. Often, this is a matter of weighing the effectiveness of intervention against the potential health effects of exposure. Historically blood lead intervention levels have been based on health risks. The absence of an identified threshold for the adverse effects of lead makes it difficult to set a blood lead intervention value that is without health risks. As a result, recent guidance recommends a "normative" approach to establishing blood lead action levels (ACCLPP, 2012). Under the normative approach, decision-making on the requirement for intervention is based on the following questions:

- Is the individual or community blood lead concentration atypical (*i.e.*, higher than normal)?

- If so, what can be done to effectively reduce the atypical exposure?

The Advisory Committee for Childhood Lead Poisoning Prevention (ACCLPP) was established by United States Centers for Disease Control and Prevention's (CDC) to provide advice and guidance to the CDC concerning recent technical and scientific advances (and their associated implications) in the area of childhood lead poisoning prevention efforts. In January of 2012, the ACCLPP presented a report to the CDC entitled 'Low Level Lead Exposure Harms Children: A Renewed Call for Primary Prevention'. The report (ACCLPP, 2012) made thirteen (13) specific recommendations. Rather than the use of a static population-based 'level of concern', the ACCLLP (2012) recommended the use of a childhood BLL reference value, representing the 97.5th percentile of BLL among children (1 – 5 years of age). It was recommended that the 97.5th percentile should be derived using the two (2) most recent cycles of the U.S., NHANES data and be re-evaluated (by the CDC) every four (4) years to ensure any changes in this sub-population (1 – 5 years of age) are correctly represented. The childhood BLL reference value is to be used to identify individual children with increased lead exposure and to help set public health goals. The current childhood BLL reference value should be set at 5 µg/dL. The ACCLLP (2012) report has placed an emphasis on primary prevention strategies (*i.e*., strategies to prevent exposures to lead) rather than responses to specific BLLs. Many of the recommendations put forth by the ACCLLP (2012) revolve around mechanisms to facilitate on-going primary prevention and reporting strategies. In a document entitled 'CDC Response to Advisory Committee on Childhood Lead Poisoning Prevention Recommendations in Low Level Lead Exposure Harms Children: A Renewed Call of Primary Prevention' (U.S. CDC, 2012), the CDC either agreed or agreed in principle (*i.e*., the CDC agreed with the recommendation but lacked the funding at this time to implement any changes) with each of the thirteen (13) recommendations put forward by the ACCLLP (2012).

Guidance contained within the two recent reports Health Canada released addressing lead that provide some insight into the direction of any forthcoming policy statements from Health Canada:

- Final Human Health State of the Science Report on Lead (February 2013)
- Risk Management Strategy For Lead (February 2013)

Both reports indicated the following:

- Blood lead levels in the Canadian population have declined significantly over the past 30 years.
- Health effects are occurring below the current Canadian blood lead intervention level of 10 µg/dL.
- Health effects have been associated with BLLs as low as 1–2 µg/dL.
- Additional measures to further reduce lead exposures to Canadians are warranted.

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