Atopic disease prevention—

A research schema for evaluating skin barrier protection and phthalate exposure reduction

Master of Public Health Capstone

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Abstract

Rationale

Globally, the prevalence of atopic diseases continues to rise. Up to 20% of the population is thought to be affected, exerting enormous health, social and financial burdens. Emerging data suggests atopic dermatitis precedes allergic sensitization and may increase the predisposition to food allergy, allergic rhinitis and asthma later in life. Pilot testing has suggested infant skin barrier protection may reduce the risk of atopic dermatitis. Parallel research has suggested exposure to phthalates may be driving the inflammatory process at the dermal level.

Methods

The altered skin barrier and hapten-atopy hypotheses are summarized. A schema for a pragmatically designed, randomized controlled trial is developed to address: 1.Does skin barrier protection using an occlusive moisturizer and measures to reduce phthalate exposure among infants reduce the incidence of atopic dermatitis and the prevalence of atopic diseases, and 2.If so, do these interventions reduce risk in an additive or synergistic manner?

Results

Population based recruitment of newborn infants to one of three interventions or a control arm is proposed. The first arm would involve the application of an occlusive skin moisturizer to protect skin barrier integrity; the second, measures to reduce dietary and environmental phthalate exposures and the third would add skin barrier protection to the phthalate exposure reduction protocol. The protocol phase would ideally continue for three years, while the observation phase for the detection of disease incidence and prevalence would span 18 years. Recommendations for data interpretation include regression analysis for modeling the intervention effects on other environmental and dietary exposures thought to increase the risk of atopic diseases.

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Conclusions

Pragmatic design would optimize the generalizability of the results. Study findings would clarify public health approaches for atopic disease prevention by broadening the current understanding of the effects of phthalates on child health and by informing best practices for infant skin care.

Background

Atopy

Atopy refers to a tendency to become immunologically sensitized to allergens ubiquitously present in the human environment by producing immunoglobulin E (IgE) antibodies against them. Allergens are proteins, capable of producing allergic (atopic) diseases in prone individuals. Capacity for producing IgE antibodies to allergens is linked to the development of atopic dermatitis (AD), food allergy, and allergic anaphylaxis, asthma, and rhinitis (Johansson et al., 2004).

Atopic individuals are likely to develop multiple allergic conditions over the course of their lifespan, beginning in childhood (Fleischer, Conover-Walker, Christie, Burks, & Wood, 2003; Peters et al., 2010). Referred to as the atopic march, clinical manifestation of atopy typically begins with AD. The incidence of AD peaks within the first three months of life, followed by food allergy later in infancy, and rhinitis and asthma later in childhood (Wahn, 2007). Moderately severe AD among infants is closely associated with IgE sensitization to foods (Hill et al., 2007) and children with AD have 3 times greater odds of developing asthma and 2.6 times greater odds of developing rhinitis compared to children without AD. Early compared to late onset, and moderate to severe compared to mild AD appear to further strengthened the association (early onset OR = 3.44, 95% CI: 1.94-6.09; moderate to severe OR = 3.56, CI: 1.62-7.83) (von Kobyletzki et al., 2012).

Prevalence and burden

Atopic diseases are the most common and earliest onset of the major non-communicable diseases and are expected to represent major public health challenges well into the 21st century

(Prescott, 2013; von Herttzen & Haahtela, 2004). In high income countries approximately 1 in 5

individuals are affected (Zheng, Yu, Oh, & Zhu, 2011) with lower socio-economic strata disproportionately

burdened (Cope, Ungar, & Glazier, 2008; Pawankar, Sanchez-Borges, Bonini, & Laliner, 2011;

Ruijsbroek et al., 2011).

Atopic dermatitis. AD causes intense itching and chronic, relapsing skin lesions characterized in

the acute stage by excoriation, inflamed dome-shaped papules and serous oozing and in the sub-acute

stage by excoriation, papules and lichenified plaques (Leung & Bieber, 2003). Lesions follow a

predictable distribution; during infancy the cheeks and scalp are usually affected, while in childhood the

nape, flexure and dorsal limb surfaces are typically involved (Bieber, 2008). Globally, the lifetime

prevalence of AD is 15 to 30% among children and 2 to 10% among adults (Bieber, 2010). Data from

Phase III of the International Study for Asthma and Allergy in Children (ISAAC) suggests AD prevalence

among children ranges from 0.9% in Jodhpur, India, to 22.5% in Quito, Ecuador. In Canada it rests at

about 10 to 15% (Odhiambo, 2009). In high income countries prevalence rose two to three fold rise over

the past three decades (Bieber, 2010) but appears to have leveled off, while it continues to rise in middle

and low income countries (Williams et al., 2008). Overall, the rise as been associated with increasing

westernization and suggests environmental factors precipitated by socio-economic changes and

urbanization are important drivers (Bieber, 2010; Romagnani, 2004).

In addition to the risk of future allergic disease, AD exerts considerable socio-economic burdens.

Families of children with AD must cope with significant emotional effects and limitations on activities of

daily living (Chamlin, Frieden, Williams, & Chren, 2004). Children with AD appear to suffer more mental

health disorders compared to children without (Chamlin, 2006) and AD is recognized as having a major

impact on child and family quality of life (Dodington, Basra, Finlay, & Salek, 2013). The economic costs of

AD are considerable. Estimates vary widely, but may be as high as $3.8 billion USD annually in the U.S.

alone (Mancini, Kaulback, & Chamlin, 2008).

Food allergy. Allergic reactions induced by food allergens can range from mild and localized to systemic and life-threatening (Lack, 2008). The U.S. National Centre for Health Statistics has estimated 4% of U.S. children have food allergy. Over the course of the decade ending in 2007, an 18% increase in the prevalence of food allergy has been reported (Branum & Lukacs, 2008). Drawing on data from several countries, a more conservative estimate suggests an increase in prevalence of 0.60% over the past 10 years (Ben-Shoshan, Turnbull & Clarke, 2012). Prescott and Allen (2011) have noted while some food allergies typically remit in childhood, newer data indicates food allergies may be persisting later into childhood (Mullins, 2007).

Food allergy has a profound impact on health-related quality of life (Avery, King, Knight, & Hourihane, 2003). Aside from the intangible costs, the economic costs of food allergy are considerable and wide ranging, from burdens on individuals and their families to regulators and healthcare systems (Miles, Fordham, Mills, Valovirta, & Mugford, 2005). A recent U.S. investigation estimated the overall annual cost of food allergy at $4184 USD per child (Gupta et al., 2013).

Anaphylaxis. Allergic anaphylaxis is an acute, life-threatening systemic reaction (Johansson et al., 2004; Sampson et al., 2006). The lifetime prevalence of anaphylaxis is between 0.05 and 2% (Lieberman et al., 2006). The most common triggers are food allergens. Anaphylaxis is commonly under reported. According to U.S. National Electronic Injury Surveillance System data, 57% of events meeting the criteria for anaphylaxis failed to be diagnosed in emergency treatment centres in the U.S. (Phelan Ross et al., 2008). While death from anaphylaxis is considered rare, under reporting is likely (Simons, 2010).

Asthma. Asthma is an inflammatory disease of the lower respiratory tract that produces airway narrowing in response to allergen and non-allergen triggers (Global Initiative for Asthma Executive Committee, 2011; Johansson et al., 2004). Prevalence ranges from 0.7% in Macau to 18.4% in Scotland (Masoli, Fabian, Holt, & Beasley, 2004). While there is evidence of a reduction in the prevalence of

asthma symptoms in a number of high income countries (Weiland & Pearce, 2004), it continues to rise in Africa, Latin America and parts of Asia (Pearce et al., 2007). However, Anandan, Nurmatov, van Schayck, & Sheikh (2010) suggest reports of declines are derived from data that more accurately reflect declines in healthcare utilization and therefore better disease control, rather than declines in actual disease prevalence.

Asthma and asthma co-morbidities are associated with significant healthcare costs (Badadori et al., 2009). It is also the most common cause of school absenteeism and non-participation in activities that support physical, intellectual, and social development among children in the U.S. (Wang, Zhong & Wheeler, 2005). Children of lower socio-economic status, particularly in low and middle income countries are disproportionately burdened by poor control (Cope et al., 2008; Pawankar et al., 2011; Ruijsbroek et al., 2011).

Hypotheses for the rise in atopic disease prevalence

Hygiene hypothesis. The hygiene hypothesis proposed by Strachan is one of the most enduring theories for explaining the rise in atopic disease prevalence (Alcantara-Neves et al., 2012; Liu & Leung, 2006; Strachan, 1989). It posits that a lack of exposure to infectious agents in early childhood, consistent with 20th century socio-economic changes, cleanliness behaviours and increasing urbanization, predisposes the immune system to a T-helper 2 (Th2) response that favours an atopic rather than a toleragenic T-helper 1 (Th1) response to allergens (Elston, 2006). Alfvén et al. (2006) demonstrated that children growing up in a farm environment were protected from atopic dieseases later in life. Children living in helminth endemic regions and younger children raised in larger families also appear to be protected. However, findings are not completely consistent: some studies suggest children growing up on farms are paradoxically at greater risk of asthma later in life (Elston, 2006). While life long farm exposure may be protective against allergic asthma in adulthood (Douwes et al., 2007), Hoppin et al. (2008) found pesticide use on farms was associated with allergic asthma among women who worked on farms, particularly those who had grown up on a farm. Endotoxin and fungal spore exposure has also been

associated with an increased risk of non-allergic asthma among farmers (Eduard, Douwes, Omenaa, & Heederik, 2004).

Altered skin barrier hypothesis. Newer findings suggest AD may not be an atopic condition; rather that it predisposes to atopic diseases (Simpson, Eichenfield, Ellis, Mancini, & Paller, 2012). Early development of AD precedes the production of IgE antibodies and other atopic diseases (Johansson & Bieber, 2002; Kubo, Nagao, & Amagai, 2012; Leung & Bieber, 2003). Recently discovered, filaggrin loss of function gene mutations have been strongly linked to the development of AD. These mutations are thought to be responsible for a set of skin barrier aberrations that lead to a reduced threshold for inflammation within the skin. These aberrations include increased transepidermal water loss (TEWL) and increased penetration of substances into the skin, including allergens (Boguniewicz & Leung, 2011; Suzuki, Kodama, & Asano, 2011; Kubo et al., 2012). Filaggrin and other related gene mutations, have provided a compelling theoretical genetic basis for the atopic march, perhaps before it has even begun (Boguniewicz & Leung, 2011).

According to a meta-analysis, filaggrin mutations increase the odds of asthma (OR = 1.48, 95% CI: 1.32-1.66) and for AD associated asthma (OR = 3.29, 95% CI: 2.84-3.82) (Rodriguez et al., 2009). A subsequent study found evidence of interaction between filaggrin mutations and sensitization to foods as a predictor of asthma in children who had AD during infancy (OR = 2.64, 95% CI: 1.7-3.98) (Marenholz et al., 2009). Another found increased TEWL, AD and AD severity predicted sensitization to foods, while filaggrin mutations did not (Flohr et al., 2013). Indeed, dermal exposure to peanut protein has been positively associated with peanut allergy among atopic disease prone children (Lack, Fox, Northstone, & Golding, 2004): household peanut consumption (used as a proxy for environmental peanut exposure) predicted peanut allergy in a dose-response manner, but only when infants did not consume peanut products orally (Fox et al., 2009).

Hapten-atopy hypothesis. The hapten-atopy hypothesis suggests synthetic compounds are acting as adjuvants at the dermal level to potentiate the atopic inflammatory response (McFadden, Dearman, White, Basketter, & Kimber II, 2011; Takano et al., 2006). Adjuvants are low molecular weight, mostly electrophilic compounds that bind to proteins to form haptens, thereby rendering the proteins more allergenic (Beltrani, Bernstein, Cohen, & Fonacier, 2006; Dudeck et al., 2011; Gittler, Krueger, & Guttman-Yassky, 2013). Utilizing a mouse model, Scharschmidt et al. (2009) found the presence of filaggrin mutations further reduced the threshold for an inflammatory response to haptens.

A range of synthetic compounds are added to a vast array of consumer products to impart fragrance, shelf life, reduced surface tension and plasticity (Jones, 2008). Many may be acting as adjuvants, including phthalates (Takano et al., 2006). Phthalates, a class of plasticizing agents, are added to personal care products, cosmetics, polyvinyl chloride, children's toys (Bornehag et al., 2004; Petersen & Breindahl, 2000), cleaning agents, insecticides, building materials, furniture, clothing, pharmaceutical products and consumer packaging (Schettler, 2005). These diesters of benzenedicarboxylic acid remain chemically unbound when added to substances and thus leach into the surrounding environment, including food and water (Duty, Ackerman, Calafat, & Hauser, 2005; Schettler, 2005), particularly when exposed to high temperatures (National Research Council, 2008). Phthalate exposure occurs through oral, respiratory, dermal and parenteral routes. Food contaminated with phthalates from packaging is thought to be the primary exposure pathway (Koniecki, Wang, Moody, & Zhu, 2011). For more background on phthalates in Canada, see Appendix A: Phthalates.

Exposure to phthalates has increased dramatically since World War II (Bornehag et al.,2004). The rise in phthalate exposure correlates well with the rise in atopic disease prevalence (McFadden, 2010). Now considered to be wide spread, there is good evidence infants are exposed to a number of phthalates early in life (NRC, 2008).

Phthalates—a population health concern

Children are disproportionately affected by chemical exposures due to their developing organs, high metabolic rate (National Center for Environmental Research, 2007; NRC, 2008) and innate exploratory hand-to-mouth and floor play behaviours (Duty et al., 2005; Sathyanarayana et al., 2008). There is compelling evidence synthetic chemicals are contributing to a range of unanticipated chronic diseases that begin in childhood (Galvez, Forman & Landrigan, 2005; Wang et al., 2005). Indeed, it is well accepted population health has been compromised by a historical orientation to a *risk management approach* for judging safety. In the absence of sufficient evidence of harm to health, the approach has placed the burden to proof of harm on the shoulders of regulators. As a result, many substances suspected of causing harm remain in use (Briand, 2010).

Regulatory changes favouring greater health and environmental protection have emerged since the United Nations adopted the precautionary principle (United Nations, 1992). The precautionary principle is a framework intended to promote healthy policy decision making. In essence, it places emphasis on taking action to protect population health in the absence of certainty (Gilbert, 2005). Fundamentally, it places responsibility for proof of safety within the manufacturer's jurisdiction (Whiteside, 2006). In Europe for instance, where the precautionary principle has being widely adopted, it has contributed to a successful ban on the importation of genetically modified crops (Whiteside, 2006). In Canada, the 2006 adoption of the Chemical Management Plan by the federal government represents a shift towards a regulatory approach in keeping with the precautionary principle (Briand, 2010). Whiteside (2006) elaborates that the precautionary principle importantly facilitates greater public participation in the regulatory decision making process and is provoking a demand for better science. He draws on work by Ulrich Beck (1992) who explains the evolution of society towards greater individualization and further away from collective goals, self-determination to protect against threats to well-being will intensify and thus reinforce the precautionary approach. Within this context, research that helps to reveal risks to the public may have greater potential to drive change in favour of stronger public health policies, particularly when disseminated and deliberated over in an open and accessible manner.

Indeed the role of phthalates to explain the rise in chronic disease is a critical and evolving public health issue and should prompt additional attention (McFadden et al., 2011). While phthalates are known for their negative effects on the developing endocrine system (Bornehag et al., 2004; Petersen, & Breindahl, 2000), they remain largely unexplored for other health effects at normal exposure levels (Koniecki et al., 2011). In support, European Academy of Allergy and Clinical Immunology has highlighted identification of causes for the rise in atopic disease prevalence, including the role of the skin barrier and environmental factors as major unmet needs in the atopy research arena (Papadopoulos et al., 2012).

Pathogenic basis for a research schema

AD stems from a defective skin barrier

The barrier function of skin, including water holding capacity, continues to develop after birth (Nikolovski, Stamatas, Kollias, & Wiegand, 2008). It is thought to function just above the threshold for AD at birth. In contrast, among infants with a predisposition to AD, it begins below this threshold and may take two and a half to three years to reach or surpass it (Cork et al., 2009).

A healthy epidermal (outer) layer of skin protects against pathogen, irritant and allergen penetration (Boguniewicz & Leung, 2011). The stratum corneum (SC), the outermost layer of the epidermis, serves as an interface and first barrier between the external environment and the fluid environment within the skin. The integrity of the SC is maintained through the constant regeneration of keratinocyte layers formed by stratum granulosum (SG) cells (Kubo et al., 2012). Filaggrin is a functional protein critically involved in this process. Produced within SG cells, filaggrin acts to collapse and compact maturing keratinocytes (Dale, Presland, Lewis, Underwood, & Fleckman, 1997; Roelandt, Heughebaert, & Hachem, 2008). Collapsed keratinocytes introduce a lipid rich gel-like mortar into the intercellular space, creating a tight, yet flexible protective outer SC layer. The mortar contains ceramides, cholesterol, cholesterol esters and fatty acids (Cork et al., 2009). Filaggrin itself is subsequently degraded into substances that acidify and hydrate the upper layer of the SC (Boguniewicz & Leung, 2011; Cork et al., 2009). Using data collected from a cohort of infants selected from the general population, of which 24.9%

had AD, Flohr et al. (2013) found filaggrin mutations predicted higher TEWL and were associated with more severe AD: the odds for AD among those with, compared to those without, the mutation were strikingly higher (OR = 3.55, 95% CI: 2.16-5.84).

AD stems from a defective immune response

There is evidence of an altered dermal immune response among individuals at risk of developing AD. Langerhans cells (LC), a class of dendritic cell, belonging to the innate immune system act to detect, engulf and present allergens and haptens to the adaptive immune system T-cells (Gittler et al., 2013). Under normal conditions, the LC remain situated below the tight junction layer within the SG. Once activated, LC are capable of triggering naïve lymphoid T-cells to mature into Th2 cells, which serve to perpetuate the atopic pro-inflammatory response (Werfel, 2009), see Figure: Atopic dermatitis stems from a defective immune response.

Chemical or mechanical disruption of the SC stimulates keratinocytes to produce cytokines; including thymic stromal lymphopoietin (TSLP)—a potent pro Th2 chemokine (Soumelis et al., 2002), which has been described as the link between innate and adaptive immunity (Ma et al., 2009). TSLP is not present in either adjacent normal skin or intact AD skin (Soumelis et al., 2002). The production of TSLP appears to be predicted by variations in TSLP gene expression (Harada et al., 2009). TSLP activates the LC to penetrate the tight junctions within the SG towards the external environment in order to engulf allergens, triggering the LC to release the Th-2 pro-inflammatory cytokines that induce T-cell maturation into Th-2 cells (Ito et al., 2005). Th-2 cells in turn produce the adaptive immune system pro-inflammatory cytokines associated with AD, including; Interleukin- 4 (IL-4), IL-13 and IL-31 (Neis et al., 2006; Werfel, 2009). In lymphoid tissue, IL-4 and IL-13 mediate B-cell production of allergen specific IgE antibodies (Werfel, 2009). The cytokines IL-4, IL-13 also act to up-regulate keratinocyte TSLP production (Gittler et al., 2013) and inhibit filaggrin production (Howell et al., 2009), while IL-31 may mediate itch (Werfel, 2009). The net result includes exacerbation of TEWL (Gittler et al., 2013).
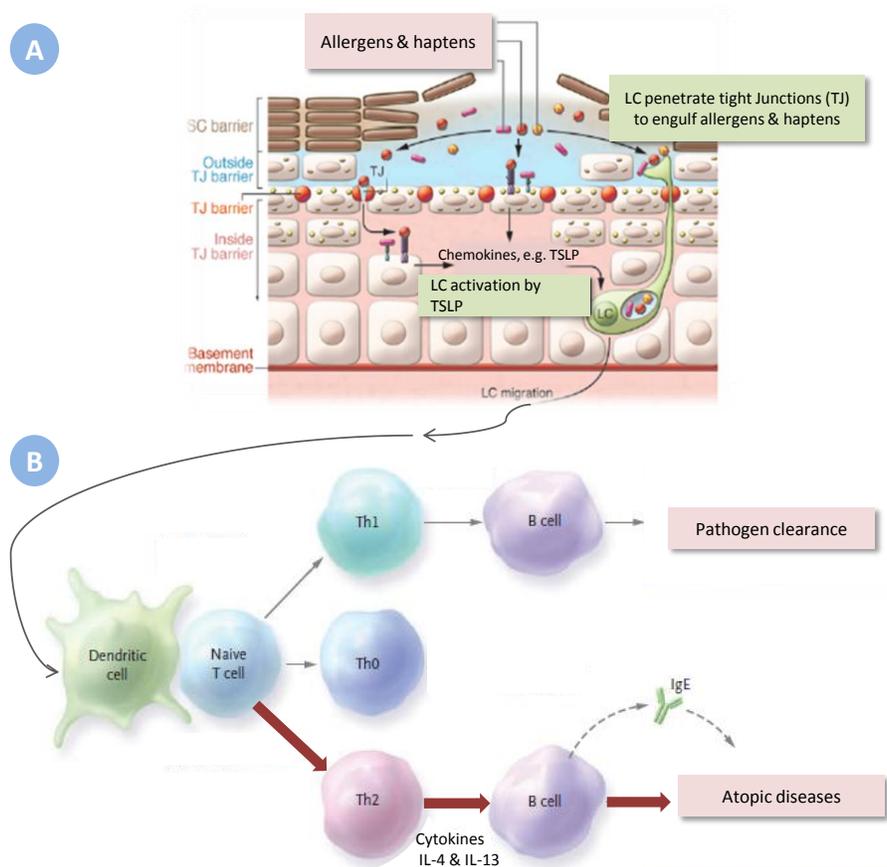
Figure: **Atopic dermatitis stems from a defective immune response**. A. In the setting of skin barrier disruption, TSLP activates langerhans cells (LC) to penetrate the tight junction layer to detect and engulf allergens and haptens that have entered the stratum corneum (SC), B. triggering naïve T-cells in lymphoid tissue to mature into Th2 cells which perpetuate the pro-topic inflammatory response. Th2 cells produce the cytokines IL-4 and IL-13 which mediate B-cell production of allergen specific IgE antibodies. Diagram A. An adaptation of a figure reproduced with permission [for educational use] from Kubo, Nagao & Amagai (2012), Copyright Journal of Clinical Investigation. Diagram B. An adaptation of a figure reproduced with permission [for educational use] from Bieber, 2008, Copyright Massachusetts Medical Society.

These recent findings, from filaggrin mutations to variations in TSLP gene phenotypic expression,

lend support to speculation that multiple factors are driving atopic responses to environmental stimuli.

Furthermore, that genetic and environmental factors may be acting either additively or synergistically to

increase risk for AD (Kubo et al., 2012).

Evidence from skin barrier protection studies

A clinic-based pilot study has been undertaken by Simpson, Berry, Brown and Hanifin (2010) to explore the feasibility of using an occlusive skin moisturizer to enhance the skin barrier integrity among infants at risk for AD. Expectant mothers were continuously recruited from the prenatal and dermatology clinics of a university health centre if their unborn infant had either a parent or related sibling with AD and one parent or sibling with either allergic asthma or rhinoconjunctivitis. The investigators noted that these infants were expected to have a 30 to 50% chance of developing AD by two years of age according to Hoare, Li Wan Po and Williams (2000). A petrolatum based (oil/grease>water) moisturizer was applied once daily to skin surfaces of the newborn infants starting at one to seven days of life. Findings included 85% compliance at 24 months of age and no adverse effects. TEWL and skin capacitance remained within normal limits, see Appendix B: Transepidermal water loss and skin capacitance measurement. The AD incidence rate was 22.7% at 18 months according to intention-to-treat analysis. These results were considered promising given the high predicted incidence among the infants recruited (Simpson, Berry, Brown, & Hanifin, 2010). Moisturizer use among infants with healthy skin also leads to reduced TEWL (Telofski, Morello III, Correa, & Stamatas, 2012). Many caregivers use moisturizers to treat infant skin regardless of whether AD is present, however as few as 12-15% attending a university based dermatology practice used thick (oil/grease> water) products with occlusive barrier properties capable of reducing TEWL (Rendell et al., 2011). Thus a skin barrier protective protocol using an occlusive moisturizer appears effective for reducing TEWL, and most likely represents a departure from conventional infant skin care practices. The selection of skin moisturizers available in the retail market is vast; not all products are equally effective or safe for infant use. Some contain phthalates (Duty et al., 2005; Sathyanarayana et al., 2008) as scent stabilizers (U.S. Department of Health & Human Services, 2013a), humectants and emollients (Hubinger & Havery, 2006).

Phthalates as drivers of AD inflammation

Evidence suggests prolonged, repeated, low dose exposures to adjuvants promotes a Th2

dominant response in the skin precipitated by TSLP (Hirasawa et al., 2009) and involves LC,

keratinocytes, and other Th2 cells (McFadden et al., 2011).

In the mouse model diisononyl phthalate (DINP) was found to activate dendritic cells, induce

TSLP production and aggravate AD in the presence of dust mite allergen. The dose that provoked the

most prominent response was at the no observable adverse effect level (NOAEL) for general chronic oral

toxicity and 6.5 to 12.5 times below the NOAEL for developmental toxicity in rats (Koike et al., 2010). Di-

(2)-ethylhexyl phthalate (DEHP), at a dose 100-fold lower than the NOAEL, also aggravated AD, and

increased the concentration of Th2 cytokines and Th2 cells in AD lesions (Takano et al., 2006). DEHP

injected into lactating mice enhanced the AD lesions in their off-spring. The aggravating dose was also

several folds lower than the NOAEL (Yanagisawa et al., 2008). Other teams have also demonstrated the

Th2 cascade precipitated by TSLP is enhanced by exposure to dibutyl phthalate (DBP) (Larson et al.,

2010; Shigeno, Katakuse, Fujita, Mukoyama, & Watanabe, 2008). While these studies explore the effects

of individual phthalates, there is a significant data gap regarding the effects of cumulative exposures to

phthalates and the most vulnerable periods of development (NRC, 2008).

Studies of the effects of phthalates on atopic disease development in humans are limited

primarily to observational studies of environmental exposure. von Kobyletzki et al. (2012) found a positive

association between polyvinyl floor coverings and the incidence of rhinitis among children with eczema,

(OR = 1.6, 95% CI: 1.02-2.51) and Carlstedt, Jönsson and Bornehag (2013) demonstrated polyvinyl

flooring in homes was predictive of butylbenzyl phthalate (BBP) metabolites in infant urine. Bornehag et

al. (2004) showed a positive relationship between BBP in dust samples and AD and rhinitis prevalence,

and between DEHP and asthma and in atopic children. Kolarik et al. (2008) and colleagues found a

positive relationship between the use of furniture cleaning agents and less frequent dusting (less than 2 to

3 times per week) and BBP, but not DEHP concentration in household dust, suggesting cleaning habits may reduce or alter phthalate exposure.

Dietary studies have been limited to exploring sources of phthalates and to test if interventions may be employed to reduce exposure. Data collected for the 2003 to 2004 U.S. National Health and Nutrition Examination Survey suggested dietary intake of poultry, tomato and potato positively predicted urine phthalates, while higher fruit consumption was a negative predictor (Colacino, Harris, & Schecter, 2010). In a study designed to explore infant phthalate uptake, Carlstedt et al. (2013) found formula feeding predicted higher urine levels of DEHP with evidence for a dose response relationship. In an interventional study, the effect of a five-day adherence to routine Buddhist practices including a vegetarian way of eating, produced significant reductions in phthalate exposure as determined by urine phthalate levels (Kyunghee, Kho, Park, & Kyungho, 2010). Rudel and colleagues showed phthalate ingestion can be reduced by avoiding food packaging and pre-prepared foods. Twenty individuals, including children, were provided with beverages and pre-prepared foods made from fresh, organic ingredients without the use of plastic utensils and containers. Post intervention urine phthalate was approximately 50% lower compared to pre-intervention levels (Rudel et al., 2011). In contrast, Sathyanarayana et al. (2013) found in another dietary intervention study, designed to reduce phthalate exposure through the provision of catered foods prepared from fresh and organic ingredients that phthalate exposure was paradoxically increased due to unexpected dairy product and spice contamination of the catered foods.

Routine infant skin care is also an important source of phthalate exposure (McFadden, 2010). Duty et al. (2005) found parent reported use of infant powder, lotion and shampoo predicted urinary excretion among infants, (OR = 2.1, 95% CI: 1.3-3.6; OR = 2.1, 95% CI: 1.3-3.4; OR = 1.6, 95% CI: 1.02-2.4, respectively). A dose response relationship was detected according to the number of skin care products used. The associations were stronger among infants younger than eight months of age (Sathyanarayana et al., 2008). Questions have been raised whether moisturizers would enhance rather

than inhibit the transmission of chemicals though the skin (Rice et al., 2003). Duty et al. (2005) found moisturizer use was associated with lower urine phthalate levels, but cautioned there is insufficient evidence to support a causal relationship.

Proposed research question

Knowledge of the possible underlying mechanisms involved and the relationship between skin barrier defects, phthalate exposure and AD development among infants suggests new research questions should be generated in order to develop existing hypotheses to explain the atopic march during different phases of the life-course. Furthermore, the health protection regulatory environment has shifted to being more conducive to uptake of research that reveals new questions about the safety of phthalates that may lead to effective interventions to reduce the hazard, thus intensifying the public health practice value of such research. The research schema that follows is designed to address the questions: Does skin barrier protection using an occlusive moisturizer and measures to reduce phthalate exposure among infants reduce the incidence of AD and the prevalence of atopic diseases later in life? If so, do these interventions reduce risk in an additive or more synergistic manner?

Experimental design considerations

Ethical considerations

To be ethical, research involving infants and children must balance, the principle that children should be protected from the potential risks of research and that they should not be excluded from the potential benefits of participation. Achieving this balance is one of the most challenging issues facing research. Interventions must be sufficiently rigorous to answer the research question posed and ensure a reasonable level of hope that they will contribute to a better understanding of disease prevention. This means a study must be adequately powered, free of important biases and lead to valid conclusions. Infants should only be recruited if the study of older individuals would fail to address the question.

Subjects should be representative of the children at risk so that the results are generalizable to the

population the research has potential to help (Diekema, 2009).

Efforts must be made to minimize the risks of participation (Diekema, 2009). Minimal risks to

healthy infants (before there is evidence of disease) is defined as risk of harm or discomfort no greater

than the "probability and magnitude…ordinarily encountered in daily life or during the performance of

routine physical…examinations or tests" (Interagency Advisory Panel on Research Ethics, 2011; U.S.

Department of Health and Human Services, 2009). When risk is greater than minimal, the benefits must

be balanced against the potential harms (IAPRE, 2011).

Given AD can begin in early infancy and the vulnerability to phthalates is also likely to be greatest

during early life, recruitment of infants according to the following schema is justifiable. The potential risks

are limited to those encountered during serial, mostly non-invasive physical examinations. Other indirect

risks include possible burdens to their parents due to extra work resulting from protocol implementation

and frustration related to limitations on food, skin care and household cleaning product selection. On the

other hand, infants whose exposure to phthalate is experimentally reduced may benefit beyond possible

reduction in AD incidence, given the potential of phthalates to adversely affect health though other

pathways, such as reproductive development (Engel et al., 2009; Swan et al., 2005). Potential benefits to

infants enrolled include; earlier detection of AD, attenuation of AD related psychological abnormalities

(Chamlin et al., 2004) and improved health-related quality of life in both subjects and their caregivers

(Lewis-Jones, Finlay & Dykes, 2001; Paller & Chren, 2012; Dodington et al., 2013).There is also the

possibility of a positive impact on parent-infant bonding stemming from the skin barrier protection protocol

(Blume-Peytavi et al., 2009).

A case for a pragmatic schema

Controlled intervention trials may be viewed as either pragmatic or explanatory. Purely pragmatic trials test whether "real world conditions" produce the desired effect (Thorpe et al., 2009). Following are some key characteristics of a pragmatically oriented research design:

- Participants recruited possess a range of risks for the condition of interest, and expected levels of protocol adherence and will vary among them (and the study is powered sufficiently to detect clinical differences given participant diversity),
- Investigators encompass a range of disciplines with a range of skills and experiences,
- There is flexibility in how and where the intervention is applied,
- The intervention is unobtrusive without measurement of compliance and without the employment, of strategies to promote adherence,
- The control arm involves usual practice rather than a placebo,
- Follow-up visits are informal and involve databases for outcome detection s,
- The primary outcome is measured and clinically meaningful to participants,
- Practitioner adherence to the protocol is either not measured or unobtrusive, and
- Analysis is according to intention-to-treat (Thorpe et al., 2009).

While very few trials are either purely pragmatic or explanatory in design, the primary advantages of a pragmatic orientation is that it tests whether the intervention will work under usual, rather than ideal conditions (Thorpe et al., 2009), hence the more pragmatic the design the better study is able to address whether the intervention is effective, rather than merely efficacious (Porzsolt, Eisemann, Habs, & Wyer, 2013).

Interventions

An experimental approach is a suitable means for exploring the effects of skin barrier protection and reduced phthalate exposure. The fundamental reasons include that existing exposure levels to phthalates may be above the levels thought to potentiate the Th2 response, thus limiting the utility of an

observational design. Likewise, given current allergy prevention recommendations do not include
guidance on skin barrier protection, current infant skin care practices are likely insufficient to optimize skin
barrier integrity according to a limited evaluation of children attending a dermatology clinic (Rendell et
al.,2011). Drawing on a population-based sample, randomly assigned, three interventions along with a
control arm should be considered; where the first involves skin barrier protection measures that can be
incorporated into routine infant care, the second phthalate exposure reduction practices, and the third
involves adding the skin barrier protection protocol to the phthalate reduction measures. The control arm
would enable detection of differences in outcomes that can be attributed specifically to the protocols,
rather than to study participation.

Protocol development and implementation

Each protocol would require substantial development by a multidisciplinary team to ensure it is a
valid, practical and safe. This may involve pilot testing. Implementation should also involve development
and delivery of an effective, standardized parent education programme to support protocol adherence
(Bieber, 2010; Futamura, Masuko, Hayashi, Ohya, & Ito, 2013; Nicol, 2011; Sathyanarayana et al., 2013).
Mid-intervention phase education to support adherence should be justified so that external validity is not
unduly compromised (Porzsolt et al., 2013). This may be accomplished by limiting education to the
frequency that could be realistically incorporated into routine prenatal and well-infants visits (Thorpe et al.,
2009).

Skin barrier protection protocol considerations. Development of the skin barrier protection
protocol would involve selection of an appropriate occlusive skin moisturizer and specification of all
aspects of infant skin care (Blume-Peytavi et al., 2012). Any moisturizers considered should be phthalate
free and as inert as possible. Pure petrolatum is a non-sensitizing (Tam & Elston 2006), widely used
moisturizer with occlusive properties (Kraft & Lynde, 2005; Nolan & Marmur, 2012). It is capable of
reducing TEWL to near normal levels (Ghadially, Halker-Sorenson, & Elias, 1992), even at concentrations
of 5% (Lynde, 2001). Occlusives introduce a hydrophobic layer on the skin surface thereby inhibiting SC

water loss. They also penetrate the SC promoting the production of intercellular lipids (Grubauer, G., Feingold, K.R. & Elias, P.M., 1987), which facilitate restoration of skin barrier function (Ghadially et al., 1992). They are particularly effective when applied directly after a bath (Telofski, L.S., Morello III, P.M., Correa, M.C.M. & Stamatas, G.N., 2012). For more background on petrolatum-based moisturizers, see Appendix C; Petrolatum-based moisturizers. Consideration should be given to pilot testing the effect of products under consideration on infant urine phthalates levels and to confirm absence of other harmful exposures. Other important moisturizer product selection criteria should include manufacturer's proof of safety, accessibility in retail markets, cost and aesthetical appeal to parents (Simpson et al., 2010). Other criteria include demonstration each individual ingredient and the product as a whole is neither irritating nor sensitizing. Products should be resistant to bacterial growth and be packaged in a manner that minimizes bacterial, as well as, chemical contamination (Telofski et al.,2012)

Phthalate exposure reduction protocol considerations. The phthalate exposure reduction protocol should address exposures resulting from infant skin care products, clothing, diapers, furniture, toys, bottles and feeding utensils, family skin care products, meals, and eating and drinking containers, food preparation utensils and storage containers, household cleaning products and practices and contact with parents' skin care products through towels and bedding. Thought should be given to ensuring study participants do not incur additional costs by implementing the protocol.

Development of a low phthalate diet for mothers, infants, and by extension the whole family, would be no small task and must balance meaningful reduction in exposure with minimal interference with normal dietary and meal planning routines to be efficacious. Low phthalate diet design criteria should include strategies for replacing foods sold and stored in cans and plastic with a wide range of alternate easy to prepare food choices and storage options. A low phthalate diet education programme should encompass parental coaching as well as instruction and the provision of supportive print and electronic resources. Current theory driven education approaches and on-line tools for promoting diet adherence may serve as useful models (Sainsbury, Mullan, & Sharpe, 2013). Valid design and implementation of the

diet may be aided by pilot testing. While the phthalate reduction protocol as described represents a significant departure from pragmatic design principles, it will optimize the efficacy of the intervention and thus strengthen the case for removal of phthalates from consumer products.

Inclusion criteria

Inclusion criteria should be limited to healthy term infants from a population unselected for AD risk to avoid over burdening infants and children already affected by illness (Diekema, 2009). Given the high prevalence of atopic diseases (Zheng et al., 2011), children without identifiable risk of AD during screening may stand to benefit from enhanced barrier protection and reduced phthalate exposure. While this will increase the number needed to recruit, it follows a pragmatic approach to study design. Furthermore, selection based on AD risk is problematic: neither parental history of atopy nor genetic testing for filaggrin mutations is very sensitive (Arshad et al., 2012). For instance, recruitment from within urban centres in Canada, will likely include some migrants from geographical regions of lower atopy prevalence. As a result, some infants at risk will not be identifiable based on parental history (Rottem, Szyper-Kravitz, & Shoenfeld, 2005).

Recruitment

Site. Generalizability of outcomes is likely favoured by a multicentre recruitment approach (Gheorghe, Roberts, Ives, Fletcher, Calvert, 2013). While more than one site complicates study administration, it supports representativeness of findings to a range of levels of urbanization, socio-demographic status, living conditions and climates. Randomization to interventions and control arms should thus occur within, not between centres.

Sample frame. Sampling is likely to be facilitated by recruiting expectant mothers wherever they may visit routinely for well pregnancy care, including; public health units and centres, family practitioner, nurse practitioner and midwifery practice offices, as well centres for prenatal diagnostic testing.

Recruitment should occur throughout the year to avoid over representation of infants exposed to AD risk factors dependent on time of year.

Study duration

Three years from birth may be considered an optimal endpoint for the protocol phase given the age at which normal skin barrier function is reached among children with a predisposition to mild AD (Cork et al., 2009). The decision on the optimal endpoint for long term outcome monitoring should be based on natural history studies of atopic disease onset and the intervals of measurement adopted by other longitudinal intervention studies to facilitate outcome comparisons. This would suggest a duration of six (Liu, Martinez, & Taussig, 2010) to 18 years after the final participant is recruited: the Isle of Wight dietary allergen and house dust mite intervention study for instance monitored participants up to 18 years of age (Arshad, Bateman, Sadeghnejad, Gant, & Matthews, 2007; Kurukulaaratchy et al., 2012; Scott et al., 2012).

 Monitoring

Adherence. Adherence monitoring should encompass all aspects of the protocols parents are asked to carry out. Protocol specific validated questionnaire instruments administered by an interviewer at specified time intervals during the intervention phase offer advantages over self-administered tools for completion rate (Neuman, 2006) and can predict adherence (Dunbar-Jacob, Sereika, Houze, Luyster, & Callan, 2012). An explanatory design approach to adherence monitoring should be considered for the phthalate reduction protocol. Adherence data may be used to offer feedback to participants to support adherence. Measurement of adherence to the dietary intervention may be undertaken using food frequency questionnaires (Rice et al., 2003). This method though subject to recall bias, may offer a better estimate of mean phthalate intake compared to 24-hour recall and duplicate diet analysis, given variability in food choices from day to day (NRC, 1993).

Primary outcomes. *Short term*. Cumulative incident AD and severity of AD between intervention and the control groups may serve as optimal primary outcome measures. Ascertainment would be best supported by direct physical examination by research assistants with standardized training and blinding to treatment (Simpson et al., 2012).

Unfortunately, a precise definition for incident AD has yet to be well defined (Simpson et al., 2012). Existing definitions are better suited for diagnosing pre-existing disease. For example, Simpson et al. (2012) note the Hanifin-Rajka criteria include "relapsing and remitting course", and the UK Working Party criteria include "itchy skin condition in the past 12 months". Therefore these definitions are ill suited for detecting new-onset cases. They have proposed a definition for incidence cases based upon the UK Working Party criteria for AD in which the duration criterion for symptoms is four weeks, see Appendix D: Proposed definition of incident AD.

A 2007 systematic review revealed only a few instruments have been developed for measuring disease severity. These include the Severity Scoring of Atopic Dermatitis Index (SCORAD), the Eczema Area and Severity Index (EASI) and the Patient–oriented Eczema Measure (POEM). All three have been adequately validated (Schmitt, Langan, & Williams & The European Dermato-Epidemiology Network, 2007). Work by the Harmonizing Outcome Measures for Eczema (HOME) initiative, an interdisciplinary group of global reach mandated to promote the advancement of eczema outcomes research (Schmitt et al., 2012), is a potential resource to assist with further refinement of a definition for AD severity.

Long term. Cumulative incidence and prevalence of other atopic diseases would serve to assess study outcomes longitudinally. Measurement of environmental allergen sensitization is also a useful predictor of atopic disease. Total house dust mites serum IgE antibodies for instance of 0.20kU/L at two years of age offered a 86.1% PPV and of 0.35kU/L at five years of age a 93.3%PPV for wheezing—an indicator of asthma (Holt et al., 2010). The definition of asthma is also complicated by phenotypic differences in disease expression. Case ascertainment would involve establishment of a measurement

protocol that accounts for these differences (Soto-Ramírez et al., 2013). Evidence of persistent wheezing rather than intermittent wheezing during the first six years of life was most predictive of asthma by 16 years of age, according to data on wheezing gathered from parental report for the Tucson Children's Respiratory Study (Martinez et al., 1995; Morgan, 2005).

First year of life incidence and subsequent prevalence of peanut allergy to five years of age may serve as useful indicators of food allergy. Peanut allergy may be measured according to a protocol described by Roberts and Lack (2005) in which parent reported signs of acute allergic reactions after peanut ingestion were validated either by skin prick or food specific serum IgE antibody test. In sum, measures of atopic disease indicators and predictors are available to detect differences in incidence and prevalence between intervention and control arms in children as early as six years of age.

Secondary outcomes. *Skin barrier integrity*. Given TEWL predicts skin barrier defects associated with AD risk, it may be a useful adjunctive measure of skin barrier protection efficacy. Guidelines for measuring TEWL have been described and utilized in other studies (Pinnagoda, Tupker, Agner, & Serup,1990). In addition, hydration of the superficial layer of the SC may be assessed by measuring skin capacitance (Matsumoto et al., 2007). However, both these measures may lack sufficient sensitivity to rule out risk of AD: Simpson et al. (2010) found the skin barrier protection protocol they investigated achieved normalization of TEWL and skin capacitance, yet a significant number of infants still developed AD.

Phthalate exposure. Cumulative and multiple as well as acute exposure to individual phthalates would serve as important variables for comparison between intervention and control groups. Högberg et al. (2008) concluded urine concentrations of phthalate metabolites in infant urine are better predictors of exposure and less invasive compared to blood and breast milk assays. Furthermore, measurement of urine phthalate metabolites may be used to assess exposure changes utilizing relatively small numbers of subjects, over short periods of time (Rudel et al., 2011).

Other exposures. An array of other exposures should be considered for monitoring during the protocol phase. Measurement of these potential co-factors could help determine whether the intervention and control groups were homogenous, and whether susceptibility to environmental exposures differs between groups. Other exposures include skin irritants, bisphenol A, environmental and food allergens, environmental tobacco smoke, household and gastrointestinal microbiomes, breastfeeding, timing and choice of weaning foods, nutrition status and climate. For summaries of each of the other exposures listed, see Appendix E: Other exposures.

While the experimental design proposed specifically involves measures to reduce phthalate exposure, it may be challenging to design a protocol that is phthalate specific: other relevant exposures are likely to be reduced as well. For instance, the household cleaning protocol proposed will most likely influence house dust mite, pet, pollen and food allergen exposures. Similarly, the skin care protocol will likely affect exposure to skin irritants and non-phthalate adjuvants unintentionally by virtue of specifying the skin care products for use. Other exposure measurement strategies should also be designed to measure changes during the invention phase: specific infant care and household cleaning practices for instance may be stopped, started or substituted during the trial.

Other outcomes. *Adverse reactions to moisturizers.* While no adverse events related to long term use of appropriate (and phthalate free) moisturizers have been identified (Simpson et al., 2010; Telofski et al., 2012), monitoring for adverse outcomes will enable characterization of the risk benefit relationship of the skin barrier protection protocol in relation to unspecified products used in the control arm and thus should be monitored.

Growth and other health outcomes. Growth velocity and attainment of adult stature is closely tied to nutrition and overall health (Garza & de Onis 2007). An increased incidence of skin infections is associated with AD (Liu et al., 2010; Novak & Leung, 2010) and an increased rate of lower respiratory tract infections have been linked to asthma (Kusel et al., 2007). Thus monitoring of growth and cumulative

incidence of infection may provide additional data for outcome evaluations. Consideration may also be given to monitoring of neurological and endocrine health to address the possibility of addition protection against disorders associated with phthalate exposure.

Genetic screening. Screening for filaggrin mutations would serve as an additional criterion for evaluating for homogeneity between intervention and control groups. It would also enable sub-group analysis of intervention effect according to AD risk (Kawaski et al., 2011). Genetic screening however has ethical implications. The psychological and social impacts of predicting future risk of disease should be considered (Geller, 2005; van El & Cornel, on behalf of the ESHG Public and Professional Policy Committee, 2011). Thus a separate consent process if genetic screening is considered may be desirable. Screening may be done with minimally invasive cheek swabs at anytime during the outcome monitoring phase with consideration given to an age at which child maturity facilitates informed consent and optimal coping with screening outcomes.

Psychological and health-related quality of life outcomes. Given the major impact of AD on health-related quality of life, measurement of differences between intervention and control groups should be considered to detect the psycho-social effects of the interventions. The Dermatitis Family Impact questionnaire and the Infants' Dermatitis Quality of Life Index (suitable for children to six years) are reliable and widely used instruments for measuring health-related quality of life outcomes that may be considered for use (Lewis-Jones et al.,2001; Van Valburg et al., 2011; Dodington et al., 2013). Unexpected positive outcomes may also occur within the psychological domain stemming from the skin barrier protection protocol. Infant bathing involves touch, is considered soothing and promotes bonding between infant and caregiver (Blume-Peytavi et al., 2009). Whether psychological benefits can be realized from the skin barrier protection protocol may be worthy of evaluation. Validated questionnaire instruments for consideration include the Maternal Postpartum Attachment Scale, the Postpartum Bonding Questionnaire and the Mother-to-Infant Bonding Scale. All three measure emotional bonding

between a mother and her infant up to approximately six months of age (van Bussel, Spitz, &

Demyttenaere, 2010).

Analysis

Differences in cumulative incidence of AD and age prevalence of severity between intervention

and control groups at defined participant ages may be compared using odds ratios of disease (Szklo &

Nieto, 2007a). Given two interventions are being tested separately and together, it is also possible to test

for additive and synergistic effects (Szklo & Nieto, 2007b).

Analysis of secondary outcomes, TEWL, skin capacitance and urinary phthalate levels would

involve two-way comparisons of means testing between independent samples using a multiple

comparison procedures and logistic regression to detect differences between the intervention and control

arms (Pagano & Gauvreau, 2000). Analysis of differences in other exposures between groups may also

be approached in a similar manner.

Regression analysis may assist to differentiate between the effects of phthalate reduction and the

protocol effects on other environmental exposures as well as the effect of the skin barrier protection

protocol on dermal phthalate and irritant exposures (Szklo & Nieto, 2007c). Differences of effect of other

exposures between interventions may also serve to develop new hypothesis concerning the relationships

between skin barrier integrity and susceptibility to the Th-2 pro-inflammatory effects of phthalate and

other environmental and dietary exposures of interest.

Sample size derivation

Anticipated sample size requirements within intervention and the control groups will depend on

the expected magnitude and variance of effects within each intervention. Actual sample size calculations

are beyond the scope of this proposal. Nonetheless, data from other longitudinal studies can assist with a

preliminary assessment of sample size requirements. Scott at el. (2012) recruited 120 at risk infants

divided between intervention and control arms to assess the effect of environmental and dietary allergen exposure reduction measures to 18 years of age. The sample was sufficient to detect a difference in overall asthma prevalence between one and 18 years of age. The unprecedented subject retention rate of 100% observed in the study cannot, however, be expected to be replicated in other settings. The Canadian Childhood Asthma Primary Prevention Study involved the recruitment of 545 at risk children before birth for evaluation post exposure intervention. At seven years 70% (approximately 190 per invention or control group) (Chan-Yeung et al., 2005) and at 15 years 60% (Wong et al., 2013) of the subjects remained available for evaluation. The average number of at risk children evaluated in nine single and multi-intervention environmental allergen exposure trials was 3271 to at least five years of age. This also represents an average of approximately 200 children per intervention arm (Maas et al., 2009), suggesting at least 200 infants unselected for atopy risk would need to be recruited for a longitudinal evaluation from birth to about five years of age.

No research was found to help estimate the anticipated magnitude of change in phthalate exposure (as determined by urine levels) necessary to affect a change in AD incidence. Sathyanarayana et al. (2008) recruited 163 infants to predict the effect of infant skin care product use on urine phthalate metabolite levels, without an intervention arm. Simpson et al. (2010) recruited 20 infants at risk of AD for assessment of a skin barrier protection protocol on AD outcomes but did not include a control group. More certainty could be added to the 200 plus figure derived from longitudinal studies by conducting controlled pilot intervention trials of both proposed protocols. Not only would they serve to develop useful data for sample size calculations, they would offer valuable lessons learned to assist with protocol refinement.

Implications of positive study findings

Study outcomes based on the outlined schema would help articulate the role of phthalates to explain the incidence and prevalence of atopic diseases and thus serve to broaden scientific understanding the effects of phthalates on child health. Furthermore, through the incorporation of

pragmatic design principles where rational, the schema would optimize the generalizability of the outcomes to the general population. Positive findings derived from the skin barrier protection protocol would offer potentially feasible approaches for optimizing best practise approaches to infant skin care guidelines disseminated through existing public health channels. Positive findings derived from the phthalate reduction arms would strengthen the evidence in favour of legislation to restrict the use of phthalates in consumer products, particularly in the context of the recent regulatory shifts in Canada. This benefit could accrue with exposure reduction alone even if no relationship to AD is found.

Positive findings would afford an opportunity to leverage (Whiteside, 2006) the precautionary principle to facilitate a deliberative process within the public domain to address synthetic compound exposures and risk to infant and child health. *Knowledge translation and exchange* could serve as a framework for facilitating this deliberative process (Boyko, Lavis, Abelson, Dobbins, & Carter, 2012). Knowledge translation and exchange is a dynamic, iterative process involving the contextualisation and integration of study findings into a larger body of knowledge on a subject. It is a systematic means for disseminating the findings to a wide audience of citizens, practitioners and policy makers through an open process employing a range of media, and is a means for exchange characterized by a collaborative problem solving approach between stakeholders and knowledge holders (Canadian Institutes of Health Research, 2013).

An "End of Grant KT" approach to dissemination (CIHR, 2013) may be taken, whereby the high prevalence and general public interest in atopic diseases is leveraged to focus on the relationship between study findings and the population health benefits of increased regulation of phthalates. Emphasis could also be directed at inclusion of a wide range of health practitioners and allergy advocacy/ interest groups to disseminated skin barrier protection findings especially within the primary and public health realms.

Schema Limitations

A major limitation to the proposed schema and common to intervention trials of longer duration is the potential for confounding. For example, indirect reduction in irritant and other hapten exposures within the skin barrier protection protocol and environmental allergen exposure within the phthalate exposure reduction protocol cannot be avoided. Even though regression analysis may help to tease out other exposure effects, the risk of colinearity is significant (Szklo & Nieto, 2007c). Considerable work would be required to develop the schema into a proposal suitable for funding and ethics applications: this work would include pilot testing and derivation of anticipated sample size requirements, as described. An estimate of the cost to carry out the schema when adequately powered to provide usable results in each of the study arm has not been provided.

Conclusions

With manifestations starting in infancy, atopic diseases are considerable public health problems that include lasting negative effects on healthy child development. While the prevalence of atopic diseases has stabilized in high income countries, regions across the globe with fewer resources to cope continue to experience rising prevalences. New hypotheses to explain complex disease origins have being articulated. The role of skin barrier impairment as a precedent to atopy and the role of phthalates as adjuvants of the pro-Th2 inflammatory response are compelling. A randomized, two-protocol, three-intervention, plus one control arm approach, with emphasis on pragmatic design, may offer a useful research schema for investigating the role of skin barrier protection and phthalate exposure reduction among infants at risk of atopic disease. A recently modernized chemical regulatory framework in Canada has the potential to change the legislative climate in favour of improved responsiveness to new research concerning synthetic chemical safety. A knowledge translation and exchange approach to dissemination of positive study findings may serve to drive change at the environmental health policy level as well as within the public health and primary healthcare domains in favour of risk reduction for AD and other atopic diseases.

Appendix A: Phthalates

In 2013, Health Canada revised a list of phthalates for further safety assessment (Government of Canada, 2013). While some used in cosmetic and personal care products are being phased out, others continue to contribute to the total body burden to which children and infants remain subjected.

Environment Canada identified 14 phthalates for assessment and a further 14 for possible assessment over the next five years (Environment Canada, 2013) due to evidence of their adverse effects on reproductive system development among male animals (NRC, 2008), see Table 1: Phthalates identified for review and possible review by Environment Canada. Much remains to be learned about the effects of phthalates. Of particular concern are the possible effects of cumulative exposure.

In a 2007 survey of personal care products available in Canada, phthalates were found in a wide range of products including those marketed for infant skin care (Koniecki et al., 2011). Of the 252 personal care and cosmetic products tested 39% contained phthalates. The specific phthalates detected included; diethyl phthalate (DEP), dimethyl phthalate (DMP), diisobutyl phthalate (DiBP), di-n-butyl phthalate (DnBP) and di (2-ethylhexyl) phthalate (DEHP).

Using data obtained from the Canadian Healthy Infant Longitudinal Development (CHILD) Study urine phthalate metabolites in 5000 three-month old infants was found to be associated with household use of tile cleaning agents; air fresheners; plastic storage containers and utensils used for breast milk, infant formula, food and beverages; infant skin care products, including baby wipes; and co-sleeping, due possibly to parent use of phthalate containing personal care products (Shu, 2010).

Table 1

Phthalates identified for review and possible review by Environment Canada [1]

Dicyclohexyl phthalate

Butyl cyclohexyl phthalate

Diisobutyl phthalate

Dimethyl phthalate

Dibenzyl phthalate

Diundecyl phthalate

Cyclohexyl isobutyl phthalate

Benzyl 3-isobutyryloxy-1-isopropyl-2,2-dimethylpropyl phthalate

Diisodecyl phthalate

Benzyl 2-ethylhexyl phthalate

Bis(methylcyclohexyl) phthalate

Diisononyl phthalate

Benzyl octyl phthalate

Diisoheptyl phthalate

Diethyl phthalate

Dibutyl phthalate [di-n-butyl phthalate][3]

Dihexyl phthalate

Butyl benzyl phthalate

Dioctyl phthalate [di(2-eythlexyl) phthalate][2]

Dipropyl phthalate

Diallyl phthalate

Diisooctyl phthalate

Ditridecyl phthalate

(C9-C11)Dialkyl phthalate

Mixed hexyl, octyl, decyl phthalates

Heptyl nonyl phthalate, branched and linear

Branched and linear nonyl undecyl phthalate

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[1] (EC, 2013), [2] (NRC, 2008), [3] (Koniecki et al., 2011)

Appendix B: Transepidermal water loss and skin capacitance measurement

Kottner, Lichterfeld and Blume-Peytavi (2013) describe TEWL as a critical aspect of skin barrier

function. Measurement is a routine practice in dermatology practice and research and can provide

accurate and reliable results. Evaporimeters measure the density of the flow of condensed water from

deeper layers to the surface of the skin in grams per metre squared per hour. While a normal range for

TEWL has not been identified, there is good evidence increased TEWL is associated the barrier function

of the SC layer. Lower values indicate intact or healed skin, while elevated levels are associated with skin

barrier defects (Kottner et al., 2013). TEWL is also affected by anatomical site, skin surface temperature,

exertion, emotion, as well as air convection near the skin, direct light, ambient temperature and humidity,

season, and geographical area (Pinnagoda et al.,1990; Kottner, Lichterfeld, & Blume-Peytavi, 2013). An

open chamber evaporimeter measures TEWL in open air, in a non-invasive manner. Ambient room

conditions must have little influence on the 10mm vapour layer that envelopes the skin to produce valid

readings (Pinnagoda, J., Tupker, R.A., Agner, T., & Serup, J., 1990). Results are also highly influenced

by technician training. Procedures involve placing the evaporimeter probe onto the skin, parallel to the

skin surface with the contact pressure kept low but constant for as short a period as possible

(approximately 30-45 seconds). Skin affected by AD lesions requires a longer measurement interval.

Anatomical sites for TEWL assessment should be standardized. Room temperature should be kept

between 20 to 22 ^{o}C with relative humidity and 40%. It is preferred, when practical, to complete all

measurements within one season (Pinnagoda, J., Tupker, R.A., Agner, T., & Serup, J., 1990). Seidenari

and Giusti (1995) showed a significant difference in TEWL could be detected using an evaporimeter

between the skin of healthy children, intact skin of children with AD and lesional skin of children with AD

in a sample of 100 children with AD and 21 without (Seidenari, S. & Giusti, G., 1995).

Skin capacitance measures the electrical conductivity of the SC. The higher the water content of

skin, the higher the capacitance. Capacitance is a measure of the amount of electrical charge that a

substance can hold. Corneometers measure capacitance with a non-invasive electrical probe that is

applied to the surface of skin. Measurements are obtained within 1 to 1.5 seconds. The skin capacitance

value provided by a corneometer is given in arbitrary units from 0 to 120 (Gabard, Clarys & Barel, 2006).

Seidenari & Giusti (1995) showed skin capacitance varies significantly between the skin of healthy

children, intact skin of children with AD and lesional skin of children with AD when the mean capacitance

values from eight different anatomical sites is compared.

Appendix C: Petrolatum-based moisturizers

Natural petrolatum is a mixture of crystalline and liquid hydrocarbons derived from petroleum, with a general carbon chain length over C_{25} (European Commission, N.D.). It is derived by de-waxing the residual oil extracted from petroleum through a number of refining and purification steps. Purification includes removal of polycyclic aromatic hydrocarbons (PAHs) that are thought to be carcinogenic in rats (Rawlings & Lombard, 2012; Nash, Gettings, Diembeck, Chudowski & Kraus, 1996). Chronic topical exposure to natural white petrolatum has been deemed to lack health risk based on the long history of use and absence of toxicological findings in animals and humans (Nash et al., 1996).

More recently, while rare, case reports have documented allergic contact dermatitis from petrolatum. PAHs contamination is thought to be responsible (Tam & Elston, 2006), with evidence of an epigenetic mechanism (Pacheco, 2012). Testing with various petrolatum products suggests the ability to sensitize is a brand specific phenomenon. Case reports also suggest allergic contact dermatitis may be restricted to damaged rather than intact skin (Tam & Elston, 2006). There are four types of petrolatum: natural, artificial, gatsch and synthetic. Natural, artificial and gatsch are derivatives of petroleum, while synthetic is manufactured through carbon monoxide hydrogenation of synthetic hydrocarbons. Considered free of PAHs, use of synthetic petrolatum may ensure prevention of allergic sensitization from petrolatum (Tam & Elston, 2006).

Appendix D: Proposed definition of incident AD

"A history of an itchy skin condition that is either continuous or intermittent lasting at least four weeks plus three or more of the following:

1. A history of a rash in the skin creases (folds of elbows, behind the knees, fronts of ankles, or around the neck) or on the extensor aspects of the forearms or lower legs

2. A personal history of asthma or hay fever or a history of atopic disease in a first-degree relative

3. A history of a generally dry skin since birth

4. Visible flexural dermatitis and/or visible dermatitis on the forearms or lower legs with absence of auxiliary involvement as defined by our online photographic protocol" (Simpson et al., 2012).

Appendix E: Other exposures

Irritants

Dermal irritant exposure can increase TEWL and contribute to skin inflammation particularly in AD prone individuals. Irritants provoke skin inflammation without inducing antibody production (Beltrani et al, 2006; Chew & Maibach 2006). In normal skin they produce an initial increase in TEWL, but after longer term exposure functional adaptation within the skin leads to normalization of TEWL through up-regulation of ceramide production. This adaptive process is impaired among individuals who are prone to AD (Slowdownik, Lee & Nixon, 2008).

Irritants comprise a vast array of chemical and mechanical exposures (Beltrani et al., 2006). They include detergents, solvents, oils, heat, dusts and fibres, acids and alkalis, friction, occlusion pressure, vibration and prolonged water exposure. The irritant effects of two or more substances may be additive or synergistic (Slowdownik et al., 2008).

Direct measurement of irritant exposure is problematic owing to the vast array of common irritants and the invasiveness of procedures to assess them (Wester, 2006). Exposure measurement may also be accomplished indirectly by employing validated questionnaires designed to collect infant skin care product usage data (Sathyanarayana et al., 2008).

Bisphenol A

Bisphenol A (BPA) is a synthetic compound used to harden polycarbonate plastics, epoxy resins, and to coat the inside of food and beverage containers and thermal paper (National Institutes of Health, 2013). Like phthalates, BPA leaches into water and food over time, particularly when subjected to heat. Exposure appears to be wide spread, although research on the health effects of BPA is limited (Meeker, Sathyanarayana, & Swan, 2009). Concern has been raised over the possible effects on neurological and reproductive development (U.S. Department of Health & Human Services, 2013b). In an observational study, urine BPA levels above the mean obtained from pregnant women were positively associated with

wheezing among infants at six months of age after adjustment for other exposures (OR = 2.3, 95% CI: 1.3-4.1). This suggests the possibility that BPA may be involved with the development of asthma and should be controlled for when investigating the relationship between phthalate exposure and the development of atopic diseases. BPA exposure may be measured by analysing urine concentrations (Spanier et al., 2012).

Environmental Allergens

Since the majority of time spent is within the home setting (Wu & Takaro, 2007), allergens commonly found indoors represent an important source of environmental exposure. Household inspection (Jaakkola, Quansah, Hugg, Heikkinen, & Jaakkola, 2013) and air sampling may be used to assess fungal exposures, while collection of dust from floors, furniture and linen may be analyzed to measure exposure to house dust, dust mite, animal and cockroach allergens (Gent et al., 2012).

Numerous studies have shown AD skin lesions can be provoked through the dermal application of a variety of environmental allergens; including pollen, fungi, dust mite and pet allergens (Boralevi et al., 2008; Capristo, Romei, & Boner, 2004). In a cross-sectional study, Boralevi and colleagues found infants three to 12 months of age with AD exhibited a higher prevalence of aeroallergen sensitization compared to controls without AD. Data from another cross-sectional study suggested AD symptom severity was associated with higher levels of air borne grass pollen (Krämer et al., 2005). In contrast, Asher and colleagues, in a summary of ISAAC Phase I results of ecological data, found no relationship between pollen exposure and eczema prevalence (Asher et al., 2010), suggesting the relationship between pollen exposure and AD is incomplete.

Cat exposure seems to increase risk while dog exposure may be protective against AD development (Ownby & Johnson, 2011). Ownby &Johnson (2011) point out failure to find a strong relationship may have in part been due to the population studied. In a prospective study of infants with filaggrin mutations (Bisgarrd et al., 2008), a cat in the home strongly increased the hazard ratio for AD at

one year of age (HR = 11.1, 95% CI: 3.79-32.6). The authors speculated the effect of cat ownership may

be mediated though a yet unknown factor for which cat exposure is a surrogate indicator.

The relationship between asthma and environmental allergens also does not appear to be entirely

clear. A meta-analysis of six studies suggests experimental reduction in household dust from birth is

effective in asthma prevention between one to eight years of age (MacDonald, Sternberg, & Hunter,

2007). A systematic review of nine intervention studies in which exposure to either environmental and/or

dietary allergens was implemented indicated multi (both environmental and dietary allergen reduction)

rather than single interventions were protective in children under five years (OR = 0.72, 95% CI: 0.54-

0.96) and over five years (OR = 0.52, 95% CI: 0.32-0.85).

Jaakkola and colleagues (2013) conducted a systematic review and meta-analysis of studies to

examine the relationship between mould exposure and rhinitis. Risk of allergic rhinitis was increased

significantly with visible mould in the home (OR = 1.51, 95% CI: 1.39-1.64), but not mould odour.

Environmental exposure to food allergens

Cutaneous exposure to food allergens can induce atopic sensitization (Spergel et al., 1998). Lack

(2008) suggested low dose dermal exposure to food proteins, inevitably present on a variety of household

surfaces, penetrates the skin barrier provoking a Th2 sensitizing response. Food allergens have been

shown to persist on household surfaces, including in pillow and furniture coverings even after cleaning.

Brough et al. (2013) showed peanut protein exposure may be quantified from household dust samples.

Environmental tobacco smoke

Aside from being clearly associated with risk for asthma (Ciaccio & Gentile, 2013), environmental

tobacco smoke (ETS) is thought to be an important predictor of AD development. Wang and colleagues

found prenatal ETS exposure was positively associated with physician ever-diagnosed AD at two years of

age. ETS exposure may increase the production of TSLP and thus induce a more intensely skewed Th2

inflammatory response within the skin (Wang, Chen, Lu, Chuan, & Chen, 2013). There is also evidence
ETS increases the risk of IgE antibody sensitization (Ciaccio & Gentile, 2013). Pre and postnatal ETS
exposure may be measured using validated questionnaire instruments; however urine cotinine appears to
be a more sensitive measure of childhood exposure, particularly longitudinally (Puig et al., 2008).

Microbial exposures

Different human environments, from urban child care centres to rural working farms, are
associated with contrasting household microbiomes. Prospective observational studies suggest child care
centre attendance during the first six months of life, the presence of older siblings in the home (Ball et al.,
2000) and dwelling on farms during childhood is protective against asthma and allergy (von Mutius &
Vercelli 2010). Experimental measures to reduce household microbial exposures have been associated
with increased rates of allergic sensitization (Woodcock et al., 2004). Protective factors may include
environmental exposure to farm animals, hay or grain products as early as during pregnancy, according
to a cross-sectional study which found a dose-response relationship (Douwes et al., 2008). Maier et al.
(2010) showed house dust sample microbial profiles predict the infant's immediate environment including
animal exposure and daycare attendance. The marker for microbial exposure used in many of these
studies has been endotoxin, a lipopolysaccharide cell-well component of gram-negative bacteria. It has
been demonstrated to have a strong capacity to promote Th1 over Th2 response immune responses
(Bolte et al.,2003). In sum, these data suggest the bacterial communities of the home environment can be
measured and are important predictors of atopic outcomes.

Gastrointestinal microbiome

Experimental studies in an effort to manipulate gastrointestinal bacterial flora have been under
taken to explore their effects on atopic disease development. A 2013 meta-analysis of 25 double blinded
placebo controlled randomized trials found probiotics were effective against atopic sensitization early in
life (defined as either or both positive skin prick tests and elevated specific serum IgE antibody levels)
when given pre and postnatally (RR= 0.88, 95% CI: 0.78-0.00), but not against asthma incidence (Elazab

et al., 2013). Analysis restricted to trials exploring the effect of pre- pro- and synbiotics on eczema prevention yielded 17 studies. Probiotics taken by the mother reduced AD risk (OR = 0.69, 95% CI: 62-78). Significant effects were only detected when multiple bacterial strains were trialed (Dang et al., 2013).

Timing and type of complementary foods

Breast milk when compared to formula feeding appears to be protective against AD among children with a family history of atopy (OR = 0.58, 95% CI: 0.41-0.92) (Gdalevich, Mimouni, David, & Mimouni, 2001), but not against other atopic diseases. Age of introduction of solids is also associated with atopy risk (Greer, F.R., Sicherer, S.H., Burks, A.W. & The American Academy of Pediatrics Committee on Nutrition; American Academy of Pediatrics Section on Allergy and Immunology., 2008). (DuToit and colleages (2008) found an association between age of peanut ingestion and peanut allergy after adjusting for multiple factors, including family atopic history.

Nutrition

Numerous efforts have been undertaken to explore the relationship between the quality of early nutrition, beginning in utero, and the risk for atopic diseases. Prescott (2013) has summarized them, including findings that a maternal diet during pregnancy rich in ω-3 polyunsaturated fatty acids (fish oils) is associated with reduced incidence of AD and atopic sensitization during infancy. Similarly a Mediterranean diet, rich in fish, legumes, vegetables and fruits during pregnancy is associated with protection against atopy, including asthma in childhood (Nurmatov, Devereux, & Sheikh, 2011; Prescott, 2013). The effects of vitamin D status have also been studied. However, isolating the effects of vitamin D status on the incidence is complicated by concurrent endogenous production of vitamin D triggered by exposure to sunshine. A meta-analysis on nutrient intake and allergic diseases found insufficient studies were available to draw conclusions on the relationship between vitamin D and atopic diseases other than that high intake during pregnancy was protective against childhood wheezing (OR = 0.56, 95% CI: 0.42-0.73; OR = 0.66, 95% CI; 0.52-0.88 respectively), but not asthma (Nurmatov et al., 2011).

Prenatal folic acid supplementation has been associated with epigenetic changes that may contribute to risk of asthma (Jiefte-de Jong et al., 2012). A meta-analysis however of folic acid intake during the first trimester of pregnancy did not find an association with the incidence of asthma in childhood. Heterogeneity of studies prevented conclusions from being drawn on associations with other atopic outcomes (Crider et al., 2013). Hence, there remains considerable controversy over the effect of diet quality and intakes of individual nutrients on atopic disease risk. It would thus seem prudent to monitor key aspects of dietary intakes during the proposed intervention study utilizing validated questionnaire instruments in a retrospective manner during pregnancy and in a prospective manner during infancy.

Climate

Conclusions drawn from ISAAC I suggest climatic conditions are associated with AD prevalence. Degrees latitude have been positively associated, while mean annual temperature negatively with prevalence. Design limitations prevent the independent assessment of the effect of sun exposure (Weiland, et al., 2004). Data from the 2007 National Survey of Children's Health study, suggests high mean annual relative humidity is protective, while prolonged annual requirement for indoor heating increases risk of AD (Silverberg, Hanifin, & Simpson, 2013).

In an experimental study in which children with severe AD were randomized to relocate from Norway to the Grand Canary Islands for four weeks, AD severity decreased dramatically and remained improved for three months, indicating exposure to a subtropical climate is associated with better AD control (Byremo, Rød, & Carlsen, 2006), however the study was unable to control for other exposures associated with the intervention, such as the vacation experience. In another experimental study, the effect of temperature and air flow on skin barrier integrity did not change TEWL significantly unless sodium lauryl sulphate (a known skin irritant) was applied to the skin of healthy adults for 30 minutes (Fluhr et al., 2005). In sum these studies suggest it is important to control for climate in studies aimed at the primary prevention of AD and other atopic diseases.

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