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Isocyanates and human health: Multi-stakeholder information needs and research priorities

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Additional Resources:
Isocyanates and Health Conference, April 3–4, 2013 conference presentations, abstracts and posters http://cirpd.org/resources/conferences/isocyanates2013

Government Agency Resources:
National Institute for Occupational Safety and Health Isocyanates Resources http://www.c dc.gov/niosh/topics/isocyanates/
Environmental Protection Agency Spray Polyurethane Foam http://www.epa.gov/dfe/pubs/projects/spf/spray_polyurethane_foam.html
Occupational Safety and Health Administration Isocyanates Resources https://www.osha.gov/SLTC/isocyanates/index.html
US National Library of Medicine (NLM) Haz-Map http://hazmap.nlm.nih.gov/search?search_query=isocyanates
The Institut de recherche Robert-Sauvé en santé et en sécurité du travail (IRSST). Guide for Safe Use of Isocyanates - An Industrial Hygiene Approach. http://www.irsst.qc.ca/en/-irsst-publication-guide-for-safe-use-of-isocyanates-an-industrial-hygiene-approach-rg-773.html
US National Institute of Environmental Health Sciences (NIEHS) Environmental Factor http://www.niehs.nih.gov/news/newsletter/2013/5/spotligh t-isocyanates/

Trade Organization Research Resources and Product Stewardship:
www.americanchemistry.com/adi
www.americanchemistry.com/polyurethanes
http://www.isopa.org/isopa/
http://www.diisocyanates.org/

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Abstract

Objective—Outline the knowledge gaps and research priorities identified by a broad-base of stakeholders involved in the planning and participation of an international conference and research agenda workshop on isocyanates and human health held in Potomac, Maryland in April 2013.

Methods—A multi-modal iterative approach was employed for data collection including pre-conference surveys, review of a 2001 consensus conference on isocyanates, oral and poster presentations, focused break-out sessions, panel discussions and post-conference research agenda workshop.

Results—Participants included representatives of consumer and worker health, health professionals, regulatory agencies, academic and industry scientists, labor, and trade associations.

Conclusions—Recommendations were summarized regarding knowledge gaps and research priorities in the following areas: worker and consumer exposures; toxicology, animal models, and biomarkers; human cancer risk; environmental exposure and monitoring; and respiratory epidemiology and disease, and occupational health surveillance.

On April 3–4th, 2013 an international multidisciplinary conference entitled *Isocyanates and Health: Past, Present and Future* was held in Potomac, Maryland. Following the conference, representatives of consumer and worker health research and regulatory agencies, academic and industry scientists, labor, and trade associations met to discuss opportunities to advance communication, collaboration, and research funding to better address information gaps and research priorities amongst stakeholders. The purposes of the conference and follow-up meeting were to (i) identify most current knowledge about isocyanates and discuss the important issues concerning potential exposures and worker and consumer health effects of isocyanates, including exposure monitoring, environmental controls, surveillance, and clinical management, and (ii) identify and discuss research gaps to inform future research priorities and information dissemination. This summary reports on the knowledge gaps and research priorities identified across stakeholders, and discusses the potential for greater collaboration across government, academic, industry and worker organizations to improve worker and consumer health.

What are isocyanates and why is this an important public and occupational health issue?

Diisocyanates and polyisocyanates, commonly referred to as isocyanates, are a family of highly reactive chemicals and one of the most frequently reported causes of occupational asthma. The most common isocyanates include, but are not limited to, toluene diisocyanate (TDI), methylenebis (phenyl isocyanate)(MDI), and hexamethylene diisocyanate (HDI), and related isomers, polymers, dimers, and trimers. Isocyanates react with the hydroxyl functional groups (i.e. –OH) of di- and polyols to form urethane linkages in the production of polyurethane polymers, typically as two-part systems. One part contains the isocyanate, sometimes mixed with solvents, and the other polyol part contains additional chemicals unique to that polyurethane product or application, such as catalysts, blowing agents, solvents, surfactants, and fire retardants. Isocyanates are used in an extensive range of products with widespread industrial, commercial, and retail or consumer applications.[1] Examples include flexible and rigid foams, sealants, elastomers, adhesives and coatings, including paints and varnishes. Their use is extensive and includes utilization within automotive, construction, clothing and shoe, home furnishing, medical and other industries.[2] Spray-on polyurethane foams and coatings containing isocyanates are applied on-site in end-user settings such as insulation of residential or commercial buildings and as coatings to protect cement, wood, fiberglass, and metal.

Manufacture and application of isocyanate containing products including polyurethane materials can result in inhalation and dermal exposures to isocyanate compounds. During production, processing, and curing, a variety of events and activities including accidental spills or leaks, application methods (spraying, painting or rolling) for isocyanate-containing foams or coatings, cleaning and maintenance of equipment, and off-gassing from newly applied or produced materials, create situations where exposure to isocyanates may occur.[3–6] Consumers may also apply products containing isocyanates, or may be incidentally exposed to commercial- or professional-grade products used by contractors or maintenance staff in their home or workplace.[7,8] Isocyanate compounds can also be generated from thermal decomposition of polyurethane materials, from activities such as heating or grinding polyurethane materials, welding of metal with polyurethane coating, cutting polyurethane foams using hot wire cutting methods, or drilling, soldering, sawing, or sanding of polyurethane materials.[9]

Isocyanates are potent sensitizers and remain one of the most commonly reported causes of occupational asthma worldwide.[10–12] The reported prevalence of isocyanate asthma in exposed workers is highly variable, ranging from less than 1% to over 30% in end-user settings such as spray applications or foam production.[13–17]

Other less commonly reported health effects include rhinitis, contact dermatitis, and hypersensitivity pneumonitis (HP).[18,19] Research, exposure monitoring and preventive efforts to-date have focused largely on inhalation exposure to diisocyanates, given that isocyanate asthma is the primary health concern. However, it is likely that skin exposure also is a highly effective route of sensitization and increases the risk of isocyanate asthma[20,21] Diisocyanates at relatively high concentrations are also irritants, to the mucous membranes but should be distinguished from monoisocyanates, such as methyl isocyanate, which is not a cross-linking agent, but is an extremely volatile irritant compound used in the production of pesticides. The International Agency for Research on Cancer (IARC) has classified 2,4-TDI, but none of the other diisocyanates, as a possible human carcinogen.[22] Pruett et al (2013) suggests that current data are inadequate to determine the carcinogenic potential of isocyanates in humans.[23]

Of particular concern is the utilization of isocyanate-containing materials in end-user settings by small industry and contractors, or consumers under some circumstances. Specific concerns range from lack of knowledge of potential health hazards, inadequate exposure monitoring and appropriate monitoring methodology, inadequate engineering and industrial hygiene controls, variable use of personal protective gear including proper respiratory and skin protection, and lack of periodic medical monitoring of exposed workers.[22,24–26]

Given the widespread use of isocyanates and their known health effects, a comprehensive strategy would be useful to identify data gaps and critically appraise current and future research and data dissemination needs concerning isocyanates and health. In addition, a more coordinated approach should be established to fund collaborative research directed at better understanding isocyanate exposures and health risks related to the manufacture, processing, and use of polyurethane products.

Conference planning process

The conference planning committee included representatives from the United States (US) Centers for Disease Control and Prevention, specifically, the Agency for Toxic Substances and Disease Registry, and the National Institute for Occupational Safety and Health; the US National Institutes of Health, including the National Cancer Institute, National Institute of Environmental Health Sciences, and the National Library of Medicine; the US Environmental Protection Agency; Health Canada; academic scientists; labor; and industry.

The following professional organizations and agencies participated as sponsors for the conference: American Academy of Clinical Toxicologists, American Conference of Governmental Industrial Hygienists, American College of Occupational and Environmental Medicine, American Industrial Hygiene Association, American Thoracic Society, Canadian Thoracic Society, Canadian Institute for the Relief of Pain and Disability, European Society for Environmental and Occupational Medicine, Occupational Medicine Specialists of Canada, Occupational and Environmental Medical Association of Canada, Society for Risk Analysis, and the Society of Toxicology. Organization sponsors participated in the Call for Papers and Posters.

The scientific committee represented a broad range of stakeholders who play different roles related to isocyanates and health including academic, government, industry, professional organizations and consumer and worker health representatives [see www.isocyanates2012.org for the list of scientific committee members].

The conference was organized around the following themes:

- Worker and consumer exposure issues
- Toxicology, animal models, and biomarkers
- Human cancer risk
- Environmental exposure and monitoring
- Respiratory epidemiology and disease
- Occupational health surveillance and management
- Health communication and research to practice

Identification of research priorities

The planning and scientific committee for the conference and workshop used an iterative systematic approach for identification of research priorities.

Round 1: A preliminary list of knowledge gaps and research priorities were identified by the section chairs after reviewing (i) the 2001 international consensus report on: Isocyanates[27], and (ii) a summary of knowledge gaps and research priorities arising from a multi-stakeholder meeting held in Montreal in September 2010 with US and Canadian regulators, academic and clinical stakeholders, and industry representatives. This preliminary list was then provided to section subcommittee members for their input.

Round 2: This preliminary list was translated into a series of targeted surveys relevant to the membership of each professional and agency sponsors. For instance, organizations whose focus was on toxicology were asked to review, update, revise and comment on knowledge gaps and research priorities relevant to isocyanates and toxicology. Concurrently, delegates who had registered for the conference by October 2012 were asked to provide input on those areas of their content expertise across all conference themes.

Round 3: Abstract presenters and invited speakers were asked to note, if applicable, knowledge gaps and research priorities within their abstracts and posters.

Throughout the conference, delegates were provided with opportunities to review the preliminary knowledge gaps and research priorities. This included a report of the findings arising from concurrent sessions during the conference. On the final day a plenary panel session was conducted to discuss the revised knowledge gaps and research priorities and opportunities to advance isocyanate research followed by an open audience discussion.

Round 4: After the conference the revised summary of knowledge gaps and research priorities was circulated to the full scientific committee for their review and input. Section

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chairs were responsible for taking this feedback under advisement and to update and revise the list of knowledge gaps and research priorities.

Round 5: The updated draft of the summary of knowledge gaps and research priorities was then circulated to all delegates for their final review and input. Section chairs were responsible for taking this feedback under advisement and to update and revise the list of knowledge gaps and research priorities. The knowledge gaps and research priorities within this publication reflect this iterative process.

Worker and consumer exposures

Andrew Comai, UAW & Andrea Pfahles-Hutchens, EPA

The worker and consumer exposures section addressed the use of isocyanates in many diverse industries, and the use of polyurethane products in both occupational and consumer settings. A broad range of topics were discussed, including use and effectiveness of worker protective equipment and controls, difficulties in sampling and measuring isocyanate exposures, evaluating consumer products for potential isocyanate and other chemical exposures, and the effectiveness of disseminating information about isocyanate hazards and protective measures to workers and consumers.

Several areas of knowledge gaps and research priorities were identified for worker and consumer exposures, including exposure assessment, dermal and inhalation exposures, exposure controls, testing of complex mixtures in polyurethane products, exposure characterization across an array of applications to identify appropriate controls, and hazard and risk communication. The priority theme across these areas was identifying and reducing exposures. A hierarchy of controls for workers and consumers for specific industries, settings and applications should be further developed and evaluated. These practices include: source reduction and elimination, ventilation and other engineering controls, education, signs, labels and warnings, and personal protective equipment. Potential consumer exposures should also be considered in developing these practices. Evaluating effectiveness of labeling and development of alternative forms of hazard communication are important to improve knowledge and compliance. Product testing is important in identifying and understanding potential consumer exposures to isocyanates and other chemicals related to polyurethane products. It is necessary to consider the diverse uses, application methods, formulations, environmental conditions, and curing rates of these products in order to adequately characterize and therefore reduce potential consumer exposures.

Table 1 describes knowledge gaps and research priorities related to worker and consumer exposures, many of which cut across other conference themes. Recognition and prevention or reduction of exposure is foremost in preventing adverse health outcomes among workers and consumers.

Toxicology, animal models, and biomarkers

Pertti (Bert) J. Hakkinen, NIH/NLM

This multi-themed section presented and discussed toxicity testing of isocyanates, animal models of allergic and asthmatic responses, and biomarkers of human exposure. Presenters outlined the immune and non-immune hypotheses driving past and current research efforts at understanding isocyanate toxicity and asthma pathogenesis, and highlighted seminal studies from the literature. The strengths, limitations and data gaps of current animal models, toxicity tests and biomarkers for use toward exposure and risk assessment as well as disease prevention were summarized.

Important contemporary issues were discussed in the context of historical studies that inform current occupational exposure limits. The contributions of animal models to understanding isocyanate sensitization and asthma and the importance of the route of exposure were discussed. Animal models have replicated many of the features of human isocyanate asthma, including sensitization and Th2-like airway inflammation. These models have also demonstrated that isocyanate dermal exposure is highly effective at inducing systemic sensitization, which can contribute to the subsequent development of asthma following inhalational exposure. Limitations of current animal models were also described, due in part to inherent species differences in airway structure and anatomy and the challenges in delivering isocyanate to the airways.

Contemporary approaches to detect potential exposure biomarkers were discussed. Isocyanate metabolites and isocyanate-protein conjugates have been measured in human biological samples using liquid chromatography and mass spectrometry.[28,29] Immunologic responses such as isocyanate-specific IgG and IgE have also been used as biomarkers of exposure and effect respectively in workers.[30] However, biomarker approaches have been difficult to validate, in part related to challenges in measuring workplace exposures. Uncertainty regarding the reactivity and metabolism of isocyanates in humans also continues to limit the development of exposure biomarkers.

Several knowledge gaps and research priorities were noted, which cut across other conference themes (Table 2), and may be addressed through future *in vitro* and *in vivo* studies using cell lines, animal models and/or clinical samples. Priority questions include: (i) Can animal models or other approaches (in vitro, in silico) be used to compare the effects of different types, doses and routes of isocyanate exposure to better predict human responses to isocyanates; (ii) Can such models be used to develop better biomarkers of exposure and early isocyanate asthma; (iii) What self-molecules are the major reaction targets for isocyanates following skin and airborne exposures *in vivo*; (iv) How are isocyanates metabolized and which isocyanate metabolites and biomolecules are the best biomarkers of isocyanate exposure; and (v) What are the most accurate and sensitive methods for quantification of proposed biomarkers in human serum or urine samples?

Human cancer risk

Gary Ellison, NCI

The human cancer risk section provided a discussion of the current state-of-the-science regarding isocyanates and cancer, and included a review of the relevant published literature. There are few data available regarding the human carcinogenicity of most isocyanates. The International Agency for Research on Cancer has classified TDI as possibly carcinogenic to humans based on evidence of tumors observed after gavage administration in experimental animal studies. However, no strong or consistent patterns have been observed in limited epidemiology studies, and a recent review suggested that TDI is not likely to be carcinogenic.[23] Because isocyanates cause allergic and other immune mediated respiratory disorders, there could be a role of the immune system and inflammation pathways in cancer risk.

Major areas covered during the human cancer risk section included populations at risk and data that could be used to assess carcinogenicity; dose-response and duration of exposure; and mechanisms associated with cancer development. The limited epidemiology studies to-date have been inadequate to determine the risk of cancer among individuals exposed to isocyanates in the workplace. A number of methodological issues exist within these studies, including limited exposure data, lack of dose-response, young cohorts with small numbers, short follow-up time, and limited information on smoking status. In addition, workers are exposed to complex mixtures of chemicals, including blowing agents, fire retardants, and organic solvents, which could act as confounders.

Many of the knowledge gaps and research priorities identified in the human cancer risk section overlap with those identified in other conference themes. For example, valid measurements of isocyanate exposure are essential to epidemiology research and critical in determining the potential cancer risk, if any, from isocyanate exposure. Also essential is access to populations of isocyanate-exposed workers, an important research priority that cuts across several research themes. The combination of animal models with human studies has the potential to accelerate the science concerning isocyanates and cancer risk. The latency period from onset of exposure to the appearance of cancer could be years and the development pathway could be an opportunity to understand the potential sequence of events that could lead to increased cancer risk among exposed workers. Research to understand the relation of isocyanate exposure to markers of early biological effect, like inflammatory markers, potential DNA damage, or oxidative stress should be explored longitudinally. Table 3 identifies the major areas of knowledge gaps and research priorities for human cancer risk.

Environmental exposure and monitoring

Robert P. Streicher, NIOSH

The environmental exposure and monitoring section addressed the detection and measurement of isocyanate compounds for the purposes of exposure assessment. This included methodology to address both inhalation exposure and dermal exposure. Isocyanate species of interest for exposure monitoring include not only those present in commercial isocyanate products, but also those species generated during the use of these products and during thermal degradation of polyurethane materials. The goals of this section were to understand how to improve isocyanate measurement methodologies, i.e., to make them easier, more reliable, and more encompassing.

The current state-of-the-art in air and dermal sampling and analytical methodology is summarized below. Accurate assessment of isocyanate exposures is particularly challenging and has hampered clinical and epidemiology research. Better methods to detect isocyanate exposures are critical to understanding isocyanate health effects and to preventing exposure and disease.

Air Sampling—Air sampling and analytical methods for isocyanates require reaction with derivatizing reagents during sampling to stabilize reacting isocyanates, and to increase the detectability and quantifiability of isocyanates. Most methods sample air using either a fiber filter impregnated with a derivatizing reagent or an impinger containing derivatizing reagent dissolved in an organic solvent, or both. Isocyanate species in particles or droplets are more challenging to collect than vapors. Furthermore, if the curing rate of the isocyanate system is rapid, a reagent-coated filter is not efficient in derivatizing isocyanate particles or droplets, resulting in underestimation of the isocyanate concentration. Impingers provide much better measurements in rapidly-curing systems, but are often difficult to use for personal sampling. A solvent-free denuder/filter sampling system is being evaluated as an alternative for isocyanate aerosols.

Dermal Sampling—There are currently no standardized or validated methods for sampling of isocyanate exposure on skin. Several methods, such as skin wipes, tape stripping, and interception barriers have been used in research settings. Current analytical methods for dermal sampling are generally modifications of methods for measuring isocyanates in air.

Analysis—Analysis of occupational air samples for isocyanates is usually accomplished using liquid chromatography. Many analytical methods attempt to measure isocyanate-containing oligomers in addition to the diisocyanate monomers, even though pure analytical standards for these species are not generally available. The diisocyanate monomer may be only a minor component in the system, making it essential to target higher molecular weight species for exposure assessment. In rapidly curing systems, newly formed isocyanate intermediates may be important contributors to exposure. However, current chromatographic methods are not designed to measure such species. A newly developed method that converts all aromatic isocyanate species in a sample to a single analyte for simplified quantification of total isocyanate group is under evaluation by NIOSH and partners in academia and industry.

Direct Reading—Direct reading monitors using paper-tape technology are useful in the detection of isocyanate vapors. However, they may not give accurate readings at low or high humidity, generally are not suitable for the measurement of isocyanate aerosols, and lack the sensitivity of chromatographic methods.

The knowledge gaps and research priorities for the environmental exposure and monitoring section fall into seven major areas: (i) air sampling methods, (ii) dermal sampling methods, (iii) analytical methods, (iv) direct-reading monitors, (v) co-exposures, (vi) thermal degradation products, and (vii) emissions from polyurethane products. Air sampling methods need to become easier to use, minimizing the need for impingers, enabling full-shift sampling, and capable of distinguishing vapor from particle exposure. Research on dermal sampling methodologies should include improved interception techniques rather than removal techniques that greatly underestimate exposure for rapidly curing isocyanates. Removal techniques should target relevant bound species rather than free isocyanates. Route-specific biomarkers of exposure (e.g. specific protein adducts) should be sought to distinguish dermal from inhalation exposure. Total isocyanate analytical methods should be evaluated and improved and liquid chromatography – tandem mass spectrometry should be much more widely used in isocyanate analysis for enhanced speciation and quantification. Depending on the type, direct-reading monitors need to become more sensitive, more robust, and more portable. Isocyanates and other compounds generated from thermal degradation of polyurethane represent an unrecognized and often unanticipated hazard. Recognition and characterization of such environments is a key priority. Methods to assess emissions from polyurethane products need to be improved and used to provide guidance on building re-occupancy times after installation of polyurethane product in building, such as spray foam insulation. Several of the environmental exposure and monitoring knowledge gaps and research priorities overlap with those expressed in the other themes. The most significant knowledge gaps and research priorities for environmental exposure and monitoring section are listed in Table 4.

Respiratory epidemiology and disease and occupational health surveillance

Mark Utell, Carrie Redlich, Philip Harber, and John Holland

The closely related respiratory epidemiology and disease, and occupational health surveillance sections addressed the human health effects of isocyanates including: the clinical spectrum of isocyanate-induced disease, host and exposure risk factors, diagnosis and outcomes, medical surveillance of isocyanate exposed workers, and prevention. A review of the clinical, epidemiologic and surveillance literature identified a number of key knowledge gaps and research needs. Isocyanates are potent sensitizers but there is no good test or marker for sensitization, as there is for typical high molecular weight allergens. While asthma is the most commonly recognized health effect of exposure, isocyanates also cause rhinitis and conjunctivitis, hypersensitivity pneumonitis, contact dermatitis, and chronic airflow obstruction, with variable and overlapping clinical syndromes. Isocyanate asthma can be difficult to recognize and diagnose, and non-asthma health effects are rarely evaluated. The persistence of asthma after removal from exposure and the resultant poor socioeconomic outcomes for impaired workers have been well documented. Importantly, despite the expanding use of isocyanate-containing products in numerous industries and end-user settings, epidemiology and surveillance studies of isocyanate-exposed workers under current work conditions have been very limited. Further, most isocyanate epidemiology studies, especially studies in end-user settings, have been cross-sectional, which are particularly prone to the healthy worker effect. Thus, critical unknowns such as the incidence and prevalence of isocyanate asthma under current work conditions, and which exposure and host factors modify the risk of developing isocyanate asthma remain poorly defined and are essential research priorities. Lack of such key information also hinders preventive efforts.

The occupational health surveillance section addressed available methods for screening groups of workers to detect those with possible occupational asthma, and diagnostic approaches to confirm (or rule out) occupational asthma. Current approaches are constrained by a number of factors including challenges in accurately assessing multiple isocyanate exposures, lack of surveillance of most exposed workers, lack of a readily available and accurate test for sensitization or isocyanate-induced asthma, limited availability and other concerns with specific inhalation challenge testing, adverse socioeconomic consequences of removing workers with isocyanate asthma from their current job, and lack of mandatory reporting of cases. There is also limited data on the efficacy of exposure reduction methods (e.g., ventilation, respirators, skin protection) in the workplace. Practical more short-term goals include optimizing initial screening questionnaires and lung function testing, improving consistency of detailed clinical and exposure assessment of suspect cases, and developing standardized approaches for evaluating the efficacy of screening programs.

The respiratory epidemiology and disease and occupational health surveillance knowledge gaps and research priorities, outlined in Table 5, overlap substantially with other theme areas. An essential priority is access to cohorts of isocyanate-exposed workers in different work settings, including longitudinal follow-up of workers (preferably inception cohorts given the healthy worker effect), and also coordinated workplace exposure assessment. Such access to workers and their workplaces and exposure information is critical to addressing the key essential knowledge gaps and research priorities, including defining the risks of isocyanate asthma and other health effects in different work settings, identifying exposure and host risk factors, and developing improved approaches for surveillance and prevention. Access to isocyanate-exposed workers is also essential to address key knowledge gaps and research priorities identified by the other groups, including evaluation of novel exposure methods, validation of biomarkers of exposure and disease, relationship of animal and *in vitro* study results to human health effects, and development of effective approaches to translate research to practice, such as interventions to reduce worker exposures.

Summary

Isocyanates are extensively used in numerous different commercial and consumer applications and contribute significantly to our quality of life and drive towards energy efficiency. The knowledge gaps and research priorities identified reflect the experiences, expertise, and multidisciplinary perspectives of the Isocyanate and Health Conference stakeholders and delegates. Many of the knowledge gaps and research priorities, although prioritized under a specific conference theme, were integral components to other areas, such as the need for epidemiology and surveillance studies of isocyanate-exposed workers, and improved methods to assess worker exposures. There was also recognition of the need to develop more effective processes to improve communication of potential health hazards and best prevention and control practices across different audiences, including workers and consumers, patients and health care providers, and researchers. Reducing the gaps between knowledge from basic science and clinical research and what is done in practice (e.g. training, policy, regulation) should be a dynamic informative process that improves understanding and compliance.

Important knowledge gaps and research priorities to better understand and prevent potential adverse health consequences from exposure to isocyanates were identified. It is recommended that a working group consisting of basic and clinical investigators from academic institutions, government, and industry, as well as employer, employee and consumer representatives be established to address the knowledge gaps and research priorities identified. A primary objective of the working group should be to create and facilitate funding pathways and to support collaborative interdisciplinary research to advance the science and knowledge of isocyanates, health and prevention. A secondary objective should be to coordinate collaborative approaches to communicate and implement best prevention and control practices, engaging a spectrum of stakeholders, including governments, trade associations, employers, manufacturers, labor and consumer organizations, professional societies, academic and industry scientists, and specialists in knowledge communication.

It is hoped that this Isocyanate and Health Conference and the current summary document will lead to greater collaboration across government, academic, industry, and worker organizations to advance research and knowledge regarding isocyanate exposures and health effects, and lead to improved preventive measures.

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Table 1

Worker and consumer exposures knowledge gaps and research priorities.

Major Area	Knowledge Gaps and Research Priorities
Product Testing and Exposure Characterization	• Develop improved methods and test product emissions under various environmental conditions, including thermal degradation. • Better characterize the isocyanate exposure potential to workers and consumers across the lifecycle of polyurethane products. • Consider methods and limitations in use of generic formulations for product testing.
Hazard/Risk Communication	• Improve accuracy of safety data sheets. • Improve guidance on installation and usage by workers and consumers, including guidance on building re-occupancy by the general public after application of isocyanate products. • Increase awareness of products that contain isocyanates and more effectively communicate the potential health hazards to workers and consumers. • Identify other potential hazardous chemicals that are used concomitantly with isocyanates.
Prevention of Exposure and Disease	• Develop and evaluate the effectiveness of Best Practices for workers and consumers. • Develop hierarchy of controls to reduce exposures (source reduction, engineering controls, education, personal protective equipment (PPE) in relation to application. • Develop approaches to improve compliance with PPE usage.

Table 2

Toxicology, animal models, and biomarkers knowledge gaps and research priorities.

Major Area	Knowledge Gaps and Research Priorities
Toxicology	• Develop approaches to better understand the connections between isocyanate uptake, metabolism, immunogenicity and asthma pathogenesis. • Further develop animal models to investigate the effects of different formulations, doses, and routes of isocyanate exposure. • Assess alternatives to animal studies, such as *in vitro* and/or *in silico* (computer and computational) models. • Assess the utility of new models for predicting human responses to exposure and risk assessment.
Biomarkers	• Further validate current candidate biomarkers of exposure, and assess their utility in monitoring worker exposures and disease prevention. • Identify novel biomarkers of exposure, including biomarkers that identify route of exposure (e.g. airway vs. skin exposure), and also better biomarkers of effect (e.g. isocyanate sensitization and asthma.

Table 3

Human cancer risk knowledge gaps and research priorities.

Major Area	Knowledge Gaps and Research Priorities
Populations at risk/ data collection	• Identify potential populations at risk and evaluate relationship between isocyanate exposure and markers of early biological effect, such as inflammatory markers, potential DNA damage, and oxidative stress.
Mechanisms	• Integrate *in vitro* and animal studies and human data to explore potential pathways and mechanisms. • Consider other mechanistic data to assess potential causality (e.g. chronic inflammation, immune responses).

Table 4

Environmental exposure and monitoring knowledge gaps and research priorities.

Major Area	**Knowledge Gaps and Research Priorities**
Air sampling methods	• Develop methods that are easier to use, especially for personal sampling, replacing impingers when possible. • Develop methods that can distinguish vapor from particle exposures. • Develop methods that enable sampling for the entire work shift.
Dermal sampling methods	• Develop improved dosimeters based on interception of the isocyanate. • Develop removal techniques that rely on relevant bound species, such as proteomic markers, rather than free isocyanates. • Identify route-specific biomarkers that distinguish dermal from inhalation exposure.
Analytical methods	• Evaluate and improve total isocyanate analytical methods. • Expand use of LC-MS/MS for enhanced speciation and quantification, especially for dermal samples and other complex matrices.
Direct-reading monitors	• Develop more sensitive and robust monitors, including faster response time for peak exposures. • Develop smaller, more portable direct-reading mass spectrometers.
Co-exposures	• Develop sampling and analytical methods to investigate the impact of co-exposures (solvents, catalysts, etc.) on dermal and respiratory isocyanate exposure uptake and responses.
Measurement of thermal degradation products	• Improve recognition of activities that may generate isocyanates or other hazardous compounds by thermal degradation. • Characterize environments where thermal degradation may be important.
Measurement of emissions from polyurethane products	• Develop improved methods to measure and model the potential for emissions of isocyanates and other chemicals during and after the application of polyurethane products. • Assess emissions during and after installation under variable conditions and settings (e.g. temperature, humidity, mixing ratio, thickness). • Develop guidance for re-occupancy times and ventilation needs during and after the application of polyurethane products.

Table 5

Respiratory epidemiology and disease and occupational health surveillance knowledge gaps and research priorities

Major Area	Knowledge Gaps and Research Priorities
Epidemiology studies of isocyanate exposed workers	Access to cohorts of isocyanate exposed workers in different work settings, and workplace exposure assessment, to determine: • Risk of isocyanate asthma and other health effects in different work settings. • Exposure risk factors (skin, airborne, peak exposures, co-exposures). • Host risk factors (other diseases, acquired, genetic). • Biomarkers of exposure and early disease (banked blood from representative-exposed cohorts for biomarkers and epidemiology studies).
Clinical spectrum and diagnosis of isocyanate asthma, other health effects	• Better characterization of isocyanate health effects and overlap syndromes: asthma, rhinitis, HP, chronic obstructive pulmonary disease, dermatitis. • Develop better diagnostic tests, including accurate tests for isocyanate sensitization, and determine the optimal role of available clinical tests, such as the clinical history, isocyanate specific antibody testing, spirometry and peak flow recordings, and nonspecific and specific inhalation challenge testing.
Surveillance of isocyanate exposed workers	• Evaluate different medical surveillance approaches, including questionnaires (specific questions), spirometry and potential changes over time, and biomarkers in order to optimize the frequency and content of surveillance. • Evaluate the effectiveness of preventive interventions such as workplace controls, product changes, PPE (respirators, gloves, clothing) to reduce exposures (isocyanates and co-exposures) and disease. • Evaluate the cost-effectiveness of different surveillance and management approaches. • Evaluate obstacles to surveillance – disincentives and incentives • Improve clinicians' and workers' awareness of isocyanate health effects, the varied clinical presentations, and preventive actions.