Residual Isocyanates in Medical Devices and Products: A Qualitative and Quantitative Assessment

Gillian Franklin[1,6], Homero Harari[2,7], Samavi Ahsan[1,8], Dhimiter Bello[2], David A. Sterling[1], Jonathan Nedrelow[3], Scott Raynaud[4], Swati Biswas[5] and Youcheng Liu[1]

[1]Department of Environmental and Occupational Health Sciences, University of North Texas Health Science Center, Fort Worth, TX, USA. [2]Department of Work Environment, University of Massachusetts at Lowell, Lowell, MA, USA. [3]Neonatal Intensive Care Unit, Cook Children's Hospital, Fort Worth, TX, USA. [4]Research Administration, Cook Children's Hospital, Fort Worth, TX, USA. [5]Department of Mathematical Sciences, University of Texas at Dallas, Richardson, TX, USA. *Current Affiliation*: [6]Postdoctoral Research Fellow, Department of Environmental Health, Harvard T.H. Chan School of Public Health, Boston, MA, USA. [7]Department of Environmental Medicine and Public Health, Icahn School of Medicine at Mount Sinai, New York, NY, USA. [8]CACI International Inc., Arlington, VA, USA.

ABSTRACT: We conducted a pilot qualitative and quantitative assessment of residual isocyanates and their potential initial exposures in neonates, as little is known about their contact effect. After a neonatal intensive care unit (NICU) stockroom inventory, polyurethane (PU) and PU foam (PUF) devices and products were qualitatively evaluated for residual isocyanates using Surface SWYPE™. Those containing isocyanates were quantitatively tested for methylene diphenyl diisocyanate (MDI) species, using UPLC-UV-MS/MS method. Ten of 37 products and devices tested, indicated both free and bound residual surface isocyanates; PU/PUF pieces contained aromatic isocyanates; one product contained aliphatic isocyanates. Overall, quantified mean MDI concentrations were low (4,4'-MDI = 0.52 to 140.1 pg/mg) and (2,4'-MDI = 0.01 to 4.48 pg/mg). The 4,4'-MDI species had the highest measured concentration (280 pg/mg). Commonly used medical devices/products contain low, but measurable concentrations of residual isocyanates. Quantifying other isocyanate species and neonatal skin exposure to isocyanates from these devices and products requires further investigation.

KEYWORDS: asthma, isocyanates, medical devices and products, methylene diphenyl diisocyanate, neonatal exposure, skin sensitization

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CORRESPONDENCE: youcheng.liu@unthsc.edu

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Background

Asthma is one of the most common and prevalent chronic childhood illnesses that causes disability, and is therefore an important area to be studied. In the United States (U.S.), self-reported asthma prevalence has significantly increased since the 1980s, and childhood asthma has more than doubled.[1,2] Asthma trend remains historically high, currently affecting about 6.2 million children under age 18.[3] This sometimes-debilitating illness places a significant health, social and economic burden on affected children, their families and society.[4] In the U.S., the estimated total economic impact of asthma in school-age children is approximately $1,993.6 million ($791 per child) in 1996.[5]

Although previous studies have identified air pollution,[6,7] indoor allergens,[8] environmental tobacco smoke,[9] and others as risk factors, and indicated the gene-environmental interactions in the causation of asthma,[10] the current knowledge of asthma causation does not fully explain the increase in asthma prevalence, pattern and disease.[11] Alternative hypotheses for asthma etiology and identifying new risk factors (epigenetic and/or environmental) that may be linked to the development of childhood asthma are priority areas of asthma causation research.[11,12] These may be necessary in developing more effective asthma prevention strategies.

In the U.S. and worldwide, rising childhood asthma prevalence parallels the increase in polyurethane (PU) and PU foam (PUF) production, and widespread use of PU/PUF products.[13] PU and PUF products contain diisocyanates, one of their primary raw material ingredients.[14] Commonly used-diisocyanates, generally referred to as "isocyanates", include aromatic toluene diisocyanate (TDI), methylene diphenylmethanediisocyanate (MDI), and aliphatic isocyanates based on hexamethylene diisocyanate (HDI) or isophorone diisocyanate (IPDI). The chemical structures of these

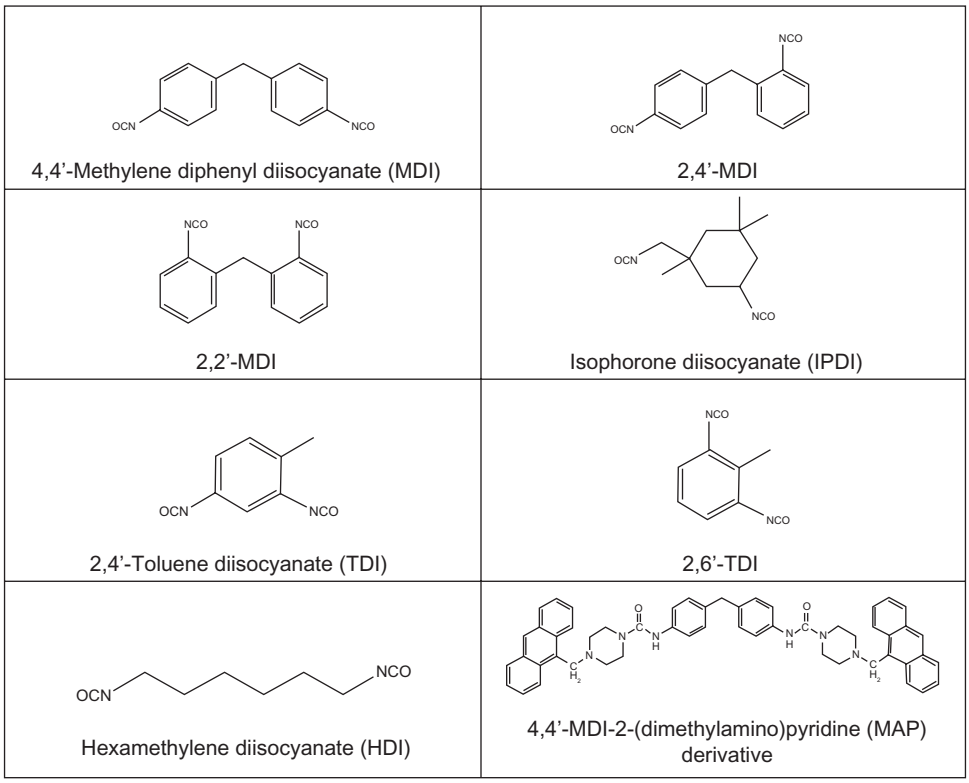


Figure 1. Diisocyanate chemical structures.

isocyanates, and their isomers are shown in Figure 1. TDI is used to make soft, flexible foams, MDI is used to make hard and rigid foams, and HDI-based isocyanates are used in paints for surface coating.[15] PU- and PUF-containing products are widely used in industries (eg, fabric-coating, paints, and insulation foams), consumer products (eg, diapers, car seats, pillows and mattresses), and medical devices (eg, neonatal SpO_2 adhesive sensors, electrodes and plaster/band).[13]

Exposure to isocyanates can induce various respiratory responses and sensitization leading to asthma,[11,16–20] confirmed mostly in occupational,[21] and non-occupational home environments where isocyanates-containing spray polyurethane foam is increasingly used as insulation.[22] Both animal and workplace epidemiologic studies indicate that dermal exposure to diisocyanates is important in respiratory sensitization, as sensitized workers can respond to low-level inhalation exposures. [16,21,23–27] According to Karol et al (as cited in Bello et al, 2007)[16] animal studies demonstrate that isocyanate skin contact could lead to sensitization, and may subsequently trigger asthmatic responses after inhalation exposure.[21]

The mechanism of sensitization leading to asthma is complex, heterogeneous, and still not well understood. The literature suggests that it is driven primarily by CD4+ T-cells, and is dependent on T-helper (Th)2 cytokines expression.[1,17,18] At birth, Th2 immune response is more dominant. As infants mature, it develops toward the adult Th1 immune response.[28] However, the presence of Th2-stimulating environmental substances (eg, food allergens) in early life could lead to increased allergic sensitization, promote the persistence of atopy, and alter the immune response toward a Th2 pattern (delay the transition to adult Th1 response) later in life, and are strongly associated with asthma.[28] Environmental exposure to isocyanates may similarly skew the neonatal Th1/Th2 balance toward a Th2 pattern, a paramount step in increasing childhood asthma incidence, especially true in genetically predisposed individuals.[13]

Few studies have been done to assess the impact of environmental exposure to isocyanates. In one study, 113 surveyed individuals living in close proximity to a PUF manufacturing factory had their blood sera analyzed from possible environmental exposure to TDI, ten (9%) developed IgG and IgE antibodies to one or more diisocyanates.[29] Newborns may be susceptible to similar environmental insults from their incomplete immunologic system, and thinner, highly penetrable skin layer, through which isocyanates may be easily absorbed. Infants may be more vulnerable, if born prematurely or have other underlining medical condition(s), ie, congenital malformation that requires hospitalization, increasing their frequency and duration in contact with medical devices and products. Therefore, it is important to evaluate if using these PU/PUF-containing medical devices and products results in skin exposure to isocyanates or subsequent sensitization.

Another study conducted in a neonatal intensive care unit (NICU) setting in New Zealand by Krone, et al (2003)

identified a small sample of medical materials (wound dressings and adhesive films) that contain isocyanate residues.[30] They postulated that dermal contact with PU-containing medical materials may be involved in dysregulation of the neonatal immune system, possibly predisposing infants to childhood asthma development.[30]

The rationale and hypothesis that contact with medical devices and other consumer products used in the NICU setting could pose a potential risk of infant skin exposure to isocyanates is that such materials may contain small amounts of unbound residual isocyanates, as well as functional isocyanate groups lingering on the surfaces, or bound in the product. Dermal exposure may result from small molecules of free unbound isocyanate monomers that may migrate to the skin surface upon prolonged contact with PU/PUF components.

The respiratory tract (inhalation) and the skin are the primary routes for isocyanate exposure, although throughout time, the inhalation route has been the focus.[16] Over time, inhalation exposures have been reduced as a result of the use of less-volatile MDI and polymeric isocyanates and improved work practices in workplaces.[16] These practices may be responsible for the relative heightened importance of skin exposure.[16] Although skin exposure assessment techniques are still in their rudimentary stage, the qualitative SWYPE pad analysis[15] and quantification methods have been developed and used to detect residual isocyanates on the skin. It is essential further studies be conducted using these methods to identify and quantify isocyanate species in medical products and possible infant skin exposure to isocyanates.

This study was the first step in evaluating NICU infants' skin exposure to isocyanates from medical devices and products, and possible risks of developing asthma later in life. The specific objectives are 1) to identify PU/PUF-containing products from the NICU inventory; 2) qualitatively/semi-quantitatively evaluate isocyanate presence/contents in selected medical devices and products, and 3) to measure the concentration of isocyanates present in the devices and products.

Methods

NICU Isocyanate-containing medical devices and products inventory. We conducted an exhaustive inventory of the medical devices and products in the stockroom used in the NICU at Cook Children's Medical Center (Fort Worth, TX, USA). A total of 134 medical devices and products routinely used in clinical settings were identified. They comprised of a large variety of medical devices and products used for various purposes and in different sizes. Information obtained included, but was not limited to, the name and catalog number of the product or device, different brands, manufacturer, intended use and any PU/PUF component displayed on the label. The detailed inventory list is outlined in Appendix I as online material.

An online search was also performed on each item to further detail the description(s) and possible safety data sheet (SDS). Furthermore, several efforts and attempts were then made to contact the manufacturers of these medical devices and products to obtain the SDS for each item, if available. Attempts were also made to obtain product information that would aid in identifying which devices and products may contain PU/PUF ingredients or components. However, the SDSs were not available for the devices and products due to "protected proprietary information" regarding the actual components in the medical devices and products.

Medical devices and products are of a wide variety, and range from things as simple as a Band-Aid to tubes and parts used on an extracorporeal membrane oxygenation (ECMO) machine and laser surgical devices.[31] Feeding tubes are commonly used to supply nutritional supplement to patients who are unable to eat. Devices with the same function are often produced by different companies or in various sizes and different brands. Several other products such as tapes come in clear and cloth varieties, as well as different sizes, 1 and ½ inches. Another example is the adhesive wound dressing film that is produced in different sizes by different companies. In addition, the foam-based infant eye protectors and phototherapy masks come in different colors (gray and black), but are produced from the same or different companies.

The objective of this step was to better select devices and products for the qualitative and quantitative testing, and to evaluate isocyanate contents from their surfaces. These are essential steps in determining the availability of isocyanates and potential skin exposure from medical devices and products.

Qualitative assessment. *Device and product selection.* From the inventory and product information assessment, thirty-seven devices and products commonly used in the NICU and possibly containing PU/PUF components were selected and qualitatively tested for surface isocyanate types and content. Tables 1 and 2 in the results section list the devices and products that were tested for aliphatic (such as HDI-based) and aromatic (such as MDI and TDI) isocyanates.

Qualitative testing method. The testing method used both aliphatic and aromatic isocyanate SWYPE™ surface sampling pads from Colormetric Laboratories, Inc. (Des Plaines, IL)[32] since the devices and products can be made of either or both types of isocyanates. The commercially prepared SWYPE™ pads for qualitative assessment are impregnated with proprietary chemicals on the pad's surface that result in a range of color change from orange to red when they come into contact with isocyanate functional groups (NCO) at different concentrations.[33] The color indication or intensity varies depending on the type and quantity of isocyanate present, and the limit of detection (LOD) for the surface SWYPE™ is 3 to 5 μg.[32] These colorimetric SWYPE™ pads have been described in various studies,[15,32,34] and validated by the Occupational Safety and Health Administration (OSHA) for industrial hygiene applications as a screening tool for assessing surface contamination by both aliphatic and aromatic isocyanates in a workplace or laboratory.[35,36]

Table 1. Isocyanate species parameters for MDI-MAP multiple reaction monitoring (MRM) transitions using UPLC-MS-MS[a].

ISOCYANATE SPECIES	PRECURSORION Q1 AMU (*m/z*)	PRODUCT ION (Q3, amu)	DT (msec)	DP (V)	EP (V)	CE (V)	CXP (V)
4,4'-MDI-MAP	803.3	191.2	250	70	5	60	5
MDI trimer	1210.8	191.2	250	90	10	100	5
MDI-d-MAP, internal standard	819.4	191.2	250	70	5	60	5

Abbreviations: [a]DT, dwell time; DP, declustering potential; EP, entrance potential; CE, collision energy; CXP, collision cell exit potential; MDI, methylene diphenylmethane diisocyanate; MAP, 1-(9-anthracenylmethyl)piperazine.

Table 2. Medical devices and products tested for isocyanates: Run 1.

SAMPLE NUMBER	DEVICE/PRODUCT NAME	RESULT		
		10 MIN	30 MIN	24 HOURS
1	Neonatal soft touch sensor	–	–	–
2	Electrode with hydrogel center	–	–	–
3	Unique electrode with hydrogel center	–	–	–
4	Film wound dressing	+	–	–
5	Nasogastric indwelling feeding tube	–	–	–
6	Enteral pump delivery sets	–	–	–
7	Type I diapers: a) inner side	–	–	–
	b) outer side	–	–	–
8	Double lumen gastric tube	–	–	–
9	Type II diaper: a) inner side	–	–	–
	b) outer side	–	–	–
10	Micro-volume extension set	–	–	–
11	Window dressing hubguard	+	–	–
12	Window dressing with small 2-part hubguard	+	–	–
13	Newborn pacifier	–	–	–
14	Medical tape (cloth)	–	–	–
15	Medical tape (clear)	–	–	–
16	Suction catheter mini tray	–	–	–
17	Neonatal pediatric monitoring electrode	–	–	–
18	Phototherapy masks (black)	–	–	–
19	Infant nipple & ring	–	–	–
20	Transparent dressing moisture vapor permeable	–	–	–
21	Pediatric urine collection bag	–	–	–
22	Baby wipes	–	–	–

To sample, the device or product was placed on a clean test bench. Top pieces from adhesive films were removed to expose the parts that would contact skin. Two devices or products of the same type were evaluated at the same time with one device/product wiped by aromatic SWYPE™ pad, and the other by aliphatic SWYPE™ pad. The method used for assessment was similar to that from an earlier study by Krone, et al (2003),[37] that evaluated PU/PUF-containing consumer products with flexible foams in which the standard procedure involved spraying the area to be sampled lightly with a developing solution (mineral oil), and waiting approximately 30 seconds for the isocyanate to dissolve before the surface was wiped with a Surface SWYPE™ pad.[38] For the current study, we followed the same modified procedure used in the prior publication[30] by applying 5 drops of acetone to the SWYPE™ pad used to wipe the surface of flat devices or surfaces of devices with irregular shapes such as an electrode. Acetone was used to help the impregnated proprietary chemical on the pads to migrate to the pads' surface, to react with isocyanates on the test items more effectively. The wiping method used similar techniques as in previous studies.[15,38,39] The surfaces were wiped with the SWYPE™ pad three times with the thumb, index and middle fingers holding the pad and pressed down firmly starting from outside moving toward

inside concentrically. Pads were then placed on the devices and products with close contact for 10 min, 30 min and 24 hours (see Tables 1 and 2). Following this step, a pastel red-orange or pink color developed, which generally occurred in 2 to 3 minutes, but sometimes it took longer. A color change on the product indicated bound isocyanates, while a color change on the wipe pad indicated free isocyanates. All devices and products that showed color change within 24 hours were recorded after two rounds (labeled "Run 1 and Run 2") of testing done one week apart. A color development either on the pad or/and on the device is considered a positive reaction.

Quantitative assessment. *Devices and products selection.* The 10 medical devices and products that tested positive qualitatively along with a few others that tested negative such as tapes were quantitatively analyzed for free, unbound, residual isocyanate species as described below. These included entire medical devices or products, some parts of the same products (ie, the foam and sensor of the neonatal SpO_2 adhesive sensor), different sizes (ie, large and small diapers) or different varieties (cloth and clear adhesive tapes) of the same products. More specifically, these included: a large diaper, a small diaper, a foam-based arm board, a neonatal SpO_2 adhesive sensor (foam portion and sensor portions), a forehead pad, foam-based infant eye protectors (large and small), Z-flo fluidized positioned cushion, an adhesive wound dressing film, a phototherapy mask, clear adhesive tape and cloth adhesive tape. The quantitative assessment focused primarily on the more common aromatic isocyanate-based PUF products as evaluated by qualitative testing.

Chemicals. 1-(9-Anthracenylmethyl)piperazine (MAP) 99+% pure, 4,4'-MDI-MAP and the internal standards (4,4'-MDI-d8-MAP) were kindly provided by Dr. Streicher's laboratory at the National Institute for Occupational Safety and Health (Cincinnati, OH, USA). Mondur MR, a well-characterized commercial aromatic diisocyanate with a total NCO content of 31.5% was used for comparison. Acetonitrile, toluene, methanol, trifluoroacetic acid and formic acid, all HPLC grade, were received from Fisher Scientific (Waltham, MA, USA).

Sample preparation and processing. Foams and suspected isocyanate-containing parts of the test items were separated from the rest of the medical devices or products. Duplicates, or two small pieces (~0.5 g, weighed accurately), each from the same device or product to be sampled, were removed (sampled), pre-weighed, and followed by an extraction method for isocyanate species using a standardized and previously published protocol.[38] The foam-type materials were placed into a glass syringe and infused with 10 mL of the 2×10^{-4} M MAP in toluene solution for one minute, and then expelled from the syringe through an Acrodisc® syringe filter (Pall Life Sciences, Port Washington, NJ, USA). The procedure was repeated ten times. A second extraction using a new aliquot of 10 mL solution (same procedure) was performed. The solution was evaporated to less than 1 mL, reconstituted to 1 mL in acetonitrile and analyzed for extractable MDI species as described below. For other materials, the product was immersed into 10 mL of 2×10^{-4} M MAP in toluene for one minute, and the procedure was repeated twice. The sample was then processed as for the syringe extraction. The rationale for using toluene is provided in the earlier paper by Vangronsveld et al.[40], whereby authors show that toluene is less likely to hydrolyze residual dimers, allophanates or the PUF foam into precursor isocyanate monomers. Although authors tested TDI-based PUF foam, the same reasoning applies to MDI-based PUF as well.

Sample analysis. The chemical analysis for isomers of MDI (4,4'-, 2,4'-, and 2,2'-), MDI trimer, and higher oligomers (tetramer and pentamer) was accomplished using the UPLC-UV-MS/MS method. The Prominence UPLC (Shimadzu, Japan) consisted of a solvent delivery unit (LC-20AB), degasser (DGU-20A3), along with an auto-sampler (SIL-20AC) and column oven (CTO-20AC). The UPLC system was attached to an Applied Biosystems–MDS SCIEX API 3200 triple quadrupole equipped with a Turbo V Ion-Spray source. Chromatographic separation was carried out on a Kinetex C18 column 100 × 4.6 mm I.D., 2.6 μm particle size (Phenomenex, CA, USA) preceded by a matching phase guard column. Separation was accomplished through a gradient elution as follows using mobile phase A: water-0.1% ammonium acetate; and mobile phase B: acetonitrile/0.1% v/v formic acid; 0.01% v/v trifluoroacetic acid. Column oven temperature was set at 40 °C. Injection volume was 10 μL. The compounds were eluted with a flow rate of 0.6 mL min^{-1} using the following gradient: 60% B to 90% B during the first 15 min, 90% to 95% B in the next 10 min (ie, from 15–25 min followed by 3 min column equilibration at 60% B). All samples were injected in duplicates, yielding four individual analyses per sample (two samples x two injections per sample). Mondur MR, a model isocyanate mixture containing the MDI monomers (4,4'-, 2,4'- and 2,2'-MDI), trimer and other oligomers was used as a reference material. Deuterated d8-MAP-MDI was used as the internal standard, which was spiked at 10 ng/mL. Chromatographic separation optimized selected reaction monitoring (SRM) transitions for each analyte and the internal standard are presented in Table 1. The optimized MS source parameters were: Curtain gas (CUR) 30, collision gas (CAD) 5, Ion spray voltage 5500, source temperature 600 PC, ion source gas 1 and 2 (GS 1, GS2) 60 and 50, respectively, and interface heater was ON.

Quantitation of MDI and trimer species was based on their respective pure standard calibrations (4,4'-MDI-MAP and MDI trimer-MAP), using MDI-d-MAP as the internal standard, spiked at 100 ng/mL. Twelve standards in the range of 250 pg/mL to 1 μg/mL MDI were routinely used for the calibration curve, determined to be linear up to 1 μg/mL ($R^2 = 0.9995$) resulting in the current LOD values. Initially, the LOD was calculated by determining the limit of the blank (LoB), as a result, the LOD = LoB + (1.645 × SD) (250 pg/mL). The calibration curve for 4,4'-MDI-MAP was linear up to

~1 μg/mL (R^2 = 0.9995). The 2,4'- and 2,2'-MDI isomers were quantitated in MS based on the calibration curve of 4,4'-MDI and a correction factor in their MS responses derived from the online UV254 detector using a series of sequential dilutions of Mondur MR. The MS correction factors were 8.70 (SD ± 0.8) and 9.6 (SD ± 1.0), respectively, for 2,4'-and 2,2'-MDI, and were used to increase the slope coefficient of the 4,4'-MDI-MAP MRM calibration curve. This implies that the MS/MS response factor for 2,4'- and 2,2'- MDI were close to an order of magnitude higher than for 4,4'-MDI. The trimer calibration curve was linear to >2 μg/mL (R^2 = 0.997), but its sensitivity in MS/MS was much lower than that of the monomer, a finding also reported by other laboratories using 2-PP reagent.[41] The LOD of MDI isomers (as 3 times the S/N ratio) were, 25 pg/mL for 4,4'-MDI, 5 pg/mL for 2,4'-MDI and ~1 ng/mL for MDI-trimer. Recovery of MDI species with this method over the calibration range was determined from independent spikes of Mondur MR and subsequent treatment as regular samples (triplicate experiments). Quality control samples included: laboratory blanks, Mondur MR, and standards – as blind samples and disclosed samples. Frequent blank injections were conducted between each sample to eliminate the likelihood of any carryover or cross-contamination between injections.

Statistical analysis. Quantities (ng) of MDI isomers from 2 injections of the same solution were averaged. Quantities from the 2 consecutive extractions of each sample were added together, and then divided by the sample weight (mg) to derive the concentration (pg/mg, equivalent to part per billion or ppb) for each replicate sample. The concentrations from the two replicate product pieces were then averaged to calculate the arithmetic mean (and standard deviation) of free extractable MDI for each device or product. Small concentrations that could not be precisely measured (ie, those concentrations below the LOD), were reported as censored values in the form of one-half of the LOD (LOD/2).[42]

Other descriptive statistics (median, and number of measurements less than LOD) were also calculated, but no hypothesis testing was performed.

Results

Qualitative assessment. For the qualitative analysis, there were two different experimental assessments conducted on same or different medical devices and products. For simplicity, these isocyanate assessment sessions were labeled "Run 1" and "Run 2".

During Run 1 depicted in Table 2, 3 of 22 (13.6%) products or medical devices showed a color change in 10 minutes, and were graded as "positive". These medical devices and/or products were film wound dressing, window dressing hubguard, and window dressing with small 2-part hubguard.

During Run 2, depicted in Table 3, 7 of 15 (46.6%) products or medical device showed a color change in 10 minutes, and were graded as "positive". These devices and/or products that showed a positive color change included the black and gray variety of phototherapy masks, diapers outside surface,

Table 3. Medical devices and products tested for isocyanates: Run 2.

SAMPLE NUMBER	DEVICE/PRODUCT NAME	RESULT		
		10 MIN	30 MIN	24 HOURS
1	Phototherapy mask (black and gray)	+	–	–
2	Type I diapers: a) inner side	–	–	–
	b) outer side	+	–	–
3	Micro-volume extension set	–	–	–
4	Infant pacifier	–	–	–
5	Foam-based IV support armboard	+	–	–
6	Film wound dressing	+	–	–
7	Neonatal SpO_2 adhesive sensor	+	–	–
8	Infant nasal seal	–	–	–
9	Medical tape (cloth): a) inner side	–	–	–
	b) outer side	–	–	–
10	Medical tape (clear): a) inner side	–	–	–
	b) outer side	–	–	–
11	Forehead pad: a) inner side	+	–	–
	b) outer side	+	–	–
12	Infant heel warmer with tape	–	–	–
13	Nasal holder clip	–	–	–
14	Neonatal fluidized positioner cushion	+	–	–
15	Soothie newborn pacifier	–	–	–

foam-based IV support arm board, film wound dressing, neonatal SpO_2 adhesive sensor, and the forehead pad, both outer and inner sides. Of note is that the film wound dressing tested positive for color change in both runs.

In 10 of the devices and products tested, 11 items were actually included, because the film wound dressing that appears in both tables 2 and 3, was counted as one product during Runs 1 and 2. A total of 10 out of 37 (27%) of the devices and products showed a positive color change between 3 minutes and 24 hours, either on the wipe pad and/or on the product surfaces indicating the presence of extractable or/and bound isocyanate functional groups.

Most of the color changes observed indicated aromatic isocyanates, such as film wound dressing which tested positive in both Run 1 and Run 2, window dressing hubguard, phototherapy mask, Type I diapers (outer side), arm board, neonatal SpO_2 adhesive sensor, and forehead pad. Only one device, the neonatal fluidized positioned cushion that was used as a bedding material indicated aliphatic isocyanates.

Figure 2 shows the results of the color change either on the product or on the wipe pad or both for seven "items" of the device/product tested in Runs 1 and 2 as depicted in Tables 2 and 3. There was observable pink or red color that indicated presence of residual isocyanates.

Quantitative assessment. Isocyanate species parameters for MDI-MAP Multiple Reaction Monitoring (MRM) transitions using UPLC-MS are outlined in Table 1, where the precursor ion and the product ions are listed. An additional MRM was not pursued in this study. A detailed description of this quantitative analytical method had been submitted for publication elsewhere (Harari et al, 2016).[43]

4,4'-MDI Concentrations. Table 4 contains details for the 13 devices and products tested. After the sample preparation was optimized, duplicate samples were analyzed to ensure the reproducibility and the robustness of this method showing the quantitative test results for the 4,4'-MDI samples. Individual concentrations (pg MDI/mg product weight) were low and variable among devices, but all measurements were above the LOD of 4,4'-MDI, 25 pg/mL. The overall concentrations were close in replicates. However, three devices had different concentrations in replicates one and two, 0.71 vs. 280 pg/mg for small diapers, 1.72 vs. 66.5 pg/mg for foam-based arm board, and 65.2 vs. 25.4 pg/mg for the foam portion of the neonatal SpO_2 adhesive sensor. These differences may reflect variations in unbound isocyanates in the product content and/or sample preparation protocols. Table 4 also shows the average extractable 4,4'-MDI concentrations in the medical devices and products. Mean (± standard deviation: SD) concentration of 4,4'-MDI ranged from 0.52 pg/mg (±0.1 pg/mg) for the forehead pad to 140 pg/mg (±100 pg/mg) for the small Type I diaper. The mean concentrations of 4,4'-MDI in other devices and products were between the mentioned ranges.

Figure 3 is a graphic representation of the mean concentrations in Table 4. Of notice are the following: small diaper, foam-based arm board, and the neonatal SpO_2 adhesive sensor, showing much higher mean 4,4'-MDI concentrations.

2,4'-MDI Concentrations. Table 5 shows the extractable 2,4'-MDI concentrations in the medical devices and products. The overall individual 2,4'-MDI concentrations were much lower than 4,4'-MDI concentrations where 28% (29/104) of the measurements had concentrations < LOD 5 pg/mL. The concentrations were also variable among devices with the overall concentrations being close in replicates. The neonatal SpO_2 adhesive sensor (foam portion) had significantly higher concentrations in both replicates (4.77 vs. 4.18 pg/mg) than other devices. Type I diaper, both large and small, had higher values in

Table 4. Extractable 4,4'-MDI concentration (pg/mg[a]) in medical devices and products.

PRODUCT NAME	REPLICATE 1[b]	REPLICATE 2	MEAN	SD[c]	NUMBER OF SAMPLES < LOD[d]
Type I diaper (large)	2.58	1.97	2.27	0.43	0/4[e]
Type I diaper (small)	0.71	280	140	197	0/4
Foam-based arm board	1.72	66.5	34.1	45.9	0/4
Neonatal SpO_2 adhesive sensor (foam portion)	65.2	25.4	45.3	28.2	0/4
Neonatal SpO_2 adhesive sensor (sensor portion)	0.691	1.26	0.98	0.41	0/4
Forehead pad	0.42	0.61	0.52	0.13	0/4
Foam-based infant eye protector (large)	17.0	16.2	16.6	0.54	0/4
Foam-based infant eye protector (small)	8.85	9.21	9.03	0.26	0/4
Neonatal fluidized positioned cushion	6.38	7.71	7.04	0.94	0/4
Adhesive wound dressing film	24.3	20.6	22.4	2.55	0/4
Phototherapy mask	9.78	9.58	9.68	0.14	0/4
Medical tape (clear)	3.97	4.47	4.22	0.36	0/4
Medical tape (cloth)	3.77	4.95	4.36	0.84	0/4

Notes: [a]pg/mg = ppb (parts per billion). [b]The number of replicates ≠ number of samples. The 2 injections from the "Sample Preparation and Processing" section above, in combination with the 2 replicates as described in the "Statistical Analysis" section above are combined, and are referred to as the "samples" (2 replicates *2 injections) = 4 samples. [c]SD: standard deviation. [d]LOD: limit of detection; 25 pg/mL for 4,4'-MDI. [e]0/4 indicates that none of the 4 samples are below (<) the LOD.

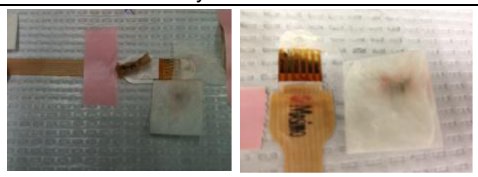
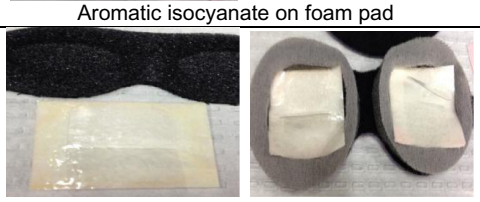
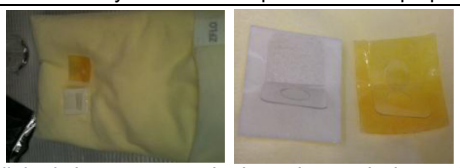
Device or product	Test result
Foam-based arm board	Aromatic isocyanates on arm board
Neonatal SPO_2 adhesive sensor	 Aromatic isocyanates on both electrode and wipe pad
Forehead pad	Aromatic isocyanate on foam pad
Foam-based infant eye protector	 Aromatic isocyanate on both product and wipe pad
Adhesive wound dressing film	Aromatic isocyanate on both product and wipe pad
Type I diaper outer side (backing)	Aromatic isocyanate on both product and wipe pad
Fluidized positioned cushion	 Aliphatic isocyanate on both product and wipe pad

Figure 2. Medical devices and products tested qualitatively for isocyanates.

replicate 2 (0.16, 0.03 pg/mg) than in replicate 1 (0.01 pg/mg). Mean (± SD) concentration of 2,4'-MDI ranged from 0.01 pg/mg for a foam-based arm board and forehead pad to 4.48 pg/mg for neonatal SpO_2 adhesive sensor (foam portion). Mean concentrations of 2,4'-MDI for other devices and products were between the mentioned range.

Figure 4 is a graphic representation of the mean 2,4'-MDI concentrations in Table 5. The following are of notice: the neonatal SpO_2 adhesive sensor, small and large foam-based infant eye protector, and the phototherapy mask had much higher concentrations than those from other devices and products.

Concentrations of Other MDI Species. The 2,2'-MDI, and MDI trimer, tetramer and pentamer were below the LOD.

Overall, quantified mean MDI concentrations were low, ranging from 0.52 to 140 pg/mg for 4,4'-MDI species and 0.01 to 4.48 pg/mg for the 2,4'-MDI species. The highest measured concentration was 280 pg/mg of the 4,4'-MDI species in small Type I diapers. The findings bring to light the fact that some

Table 5. Extractable 2,4'-MDI concentration (pg/mg[a]) in medical devices and products.

PRODUCT NAME	REPLICATE 1[b]	REPLICATE 2	MEAN	SD[c]	NUMBER OF SAMPLES < LOD[d]
Type I diaper (large)	0.01	0.16	0.08	0.10	3/4
Type I diaper (small)	0.01	0.03	0.02	1.46	2/4[e]
Foam-based arm board	0.01	0.02	0.01	0.003	2/4
Neonatal SpO_2 adhesive sensor (foam portion)	4.77	4.18	4.48	0.41	0/4[e]
Neonatal SpO_2 adhesive sensor (sensor portion)	0.04	0.01	0.02	0.02	2/4
Forehead pad	0.02	0.01	0.01	0.004	3/4
Foam-based infant eye protector (large)	3.22	3.10	3.16	0.08	0/4
Foam-based infant eye protector (small)	1.66	1.64	1.65	0.01	0/4
Neonatal fluidized positioned cushion	0.33	0.38	0.36	0.03	0/4
Adhesive wound dressing film	0.55	0.61	0.58	0.04	0/4
Phototherapy mask	1.65	0.60	1.62	0.04	0/4
Medical tape (clear)	0.12	0.21	0.16	0.06	0/4
Medical tape (cloth)	0.13	0.26	0.20	0.09	0/4

Notes: [a]pg/mg = ppb (parts per billion). [b]The number of replicates ≠ number of samples. The 2 injections from the "Sample Preparation and Processing" section above, in combination with the 2 replicates as described in the "Statistical Analysis" section above are combined, and are referred to as the "samples" (2 replicates *2 injections) = 4 samples. [c]SD: standard deviation. [d]LOD: limit of detection; 5 pg/mL for 2,4'-MDI. [e]0/4 indicates that none of the 4 samples are below (<) the LOD; 2/4 indicates that two (2) of the four (4) samples are below the LOD.

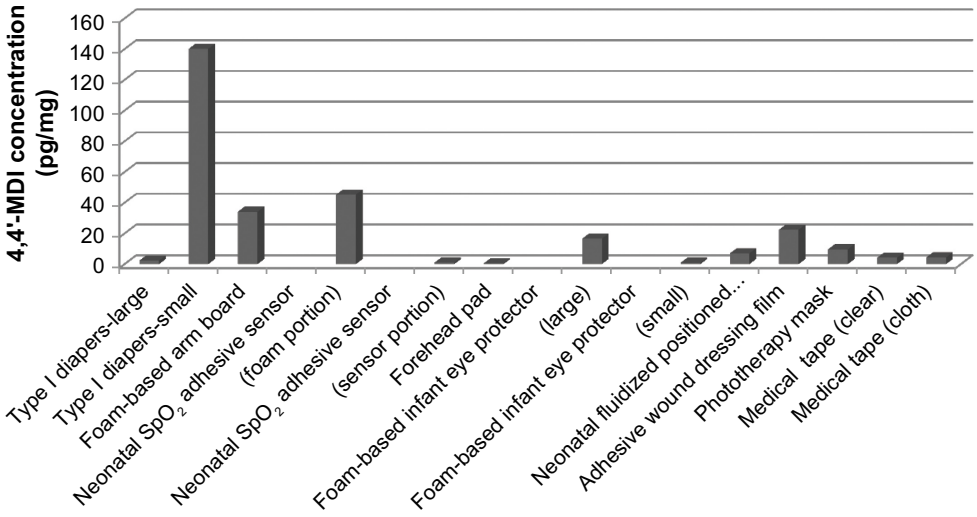


Figure 3. Mean 4,4'-MDI concentrations by device.

commonly used NICU medical devices and products reveal low but measurable concentrations of 4,4'- and 2,4'-MDI species.

Discussion

In this original study, assessment of medical devices and products for residual isocyanates included an inventory, and qualitative and quantitative measurements. This large inventory of medical devices and products allowed for a broad range of sample selection and testing. The qualitative assessment results of this study demonstrated that some medical devices and products used in the NICU setting had PU or PUF components that contained residual and/or bound isocyanates. Most PU/PUF pieces contained aromatic isocyanates, while one product contained aliphatic isocyanates. Our results are similar to those found in an earlier qualitative analysis study that looked at environmental products such as pillows, auto seats, sofas and mattresses.[37]

The medical devices and/or products identified as containing residual isocyanates were further quantitatively analyzed for the presence of MDI species. To the best of our knowledge, this is the first study that quantified isocyanates in medical devices and products. In a recent study,[44] Ramzy et al looked at commonly used cloroprene products, which is somewhat similar to our study, in that their analysis included medical devices (a medical thumb wrap, a medical wrist wrap, and two knee sport supports). However, the Ramzy et al study differs

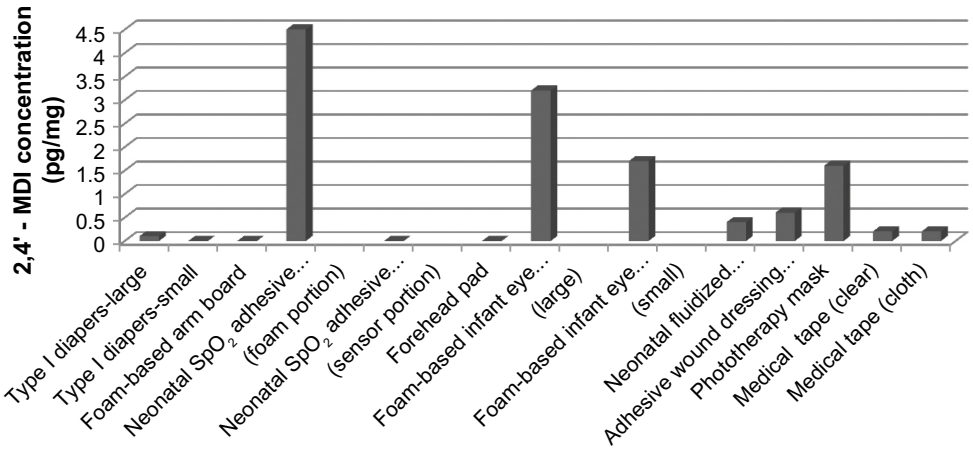


Figure 4. Mean 2,4'-MDI concentrations by device.

from the present study, since their analysis was mainly to look at the content of diethylthiourea (DETU) and ethyl isothiocyanate (EITC), and their role in skin sensitization. Although these compounds, a thiourea and an isothiocyanate [functional group N = C = S = (NCS)][44] respectively, are structurally similar to isocyanates [functional group N = C = O (NCO)][16], their chemical makeup is dissimilar. The quantitative testing not only helped confirm the presence of residual isocyanates in the medical devices and products from the qualitative assessments, but also identified the isocyanate species and measured quantities. The 4,4'-MDI species were detectable in all medical devices and products tested, while the 2,4'-MDI species were detectable in only 38% (5/13) of the tested devices. The 4,4'-MDI monomer has been found to be at 50% of a polymeric MDI mixture. The presence of 2,4'-MDI isomers in lower levels, directly corresponds to the lower amounts of 2,4'-MDI in the polymeric MDI composition. Although the concentrations for both the 4,4' and 2.4'-MDI species were low, and other MDI species were not detected, moving forward with future testing and analysis of other isocyanates such as HDI and TDI, these findings may be significant for several reasons.

First, the body's outer surface, the skin, is exposed and vulnerable to environmental insults including allergens.[45] Environmental allergens that come in contact with the epidermis may attach themselves via sweat and sebum to the surface epithelium (stratum corneum), and over time are likely to induce skin sensitization, specifically neonatal skin exposure from mechanical friction.[45] Studies suggest that protein antigens gain dermal access, and are sufficiently immunogenic, which is the basis for diagnostic testing, done by exposing the skin to protein/food allergens.[46,47]

Although none of the mechanisms that are eluded above proves primary dermal sensitization,[45] the skin is the ideal medium for de novo induction of primary immune responses, as the part of the body exposed to environmental agents.[45] Moreover, the skin is an innate immunologic organ,[48] with the most potent epithelial antigen-presenting system with the host dendritic Langerhans cell.[47,49] Langerhans cells are capable of antigen uptake, migration to local draining lymph nodes, and presenting the processed antigen to the antigen/hapten-specific T-cells.[50] However, the Langerhans cell antigen presenting system has not been determined to induce specific immune responses that would result in an allergen-specific IgE production.[45] Although the IgE mechanism for low molecular weight (LMW) substances like isocyanates, compared to high molecular weight (HMW) substances like glycoproteins and food allergens is still unknown, animal studies show that primary sensitization can take place through the skin.[45]

Second, approximately 50% of the babies admitted to a NICU are premature (J. Nedrelow, personal communication, November 24, 2014), thus having compromised skin barrier structure and function.[49] The epidermal thickness of preterm infants born at 24–30 weeks of gestation is thinner, at approximately 31 μm, versus that of a full-term infant whose epidermal thickness is approximately 43 μm.[50] That being said, the skin structure and function of all infants (premature and full-term) differ from those of adults, which may potentially put them at a higher risk for exposure to various substances, including isocyanates, well known sensitizers.[23,51–54] Moreover, LMW isocyanates such as TDI show adverse health effects in exposed workers, even at very low exposure levels.[55]

In fact, it is well established that isocyanates lead to hypersensitivity reactions,[16] and these hypersensitivity reactions can occur at very low concentrations.[56,57] Therefore, the potency of chemical allergens such as isocyanates at low concentrations may pose some potential sensitization risk to some neonates due to their compromised skin barrier function.[51] Future skin testing to evaluate transfer of unbound isocyanate species and assess skin absorption using biological monitoring is necessary.

Third, according to Heederik & Houba,[58] although epidemiological studies have demonstrated that the most important risk factor for occupational asthma is exposure level,

little is known in regards to the sensitization risks at low concentrations especially with regard to environmental allergens, and whether there is the existence of a "no-effect level". While data from several studies indicate that sensitization from IgE-mediated exposures are unlikely to occur at concentrations less than 0.5 $mg.m^{-3}$ for flour dust,[59–61] 0.7 $\mu g.m^{-3}$ for urinary rat allergens,[62] 0.6 $ng.m^{-3}$ for natural rubber latex allergens,[63] and 0.25 $ng.m^{-3}$ for fungal alpha-amylase allergens,[64] little is known on the skin dose that initiates isocyanate skin sensitization. Currently, there are no human studies confirming isocyanate skin absorption. However, animal studies have demonstrated radiolabeled isocyanates absorption after skin exposure [Leibold et al 1999; Vock and Lutz 1997, as cited in Bello et al (2007)[16]]. Moreover, evidence to support isocyanate skin absorption has been documented using infrared spectroscopy, showing isocyanates disappearance from guinea pig skin.[65] Therefore, the potential of skin exposure to isocyanates from medical devices and products should be minimized or avoided as much as possible so as to reduce skin absorption of isocyanates and their subsequent consequences.

Strengths

First, this is a novel study, in which one of the major strengths is that the medical devices and products tested were selected from a large NICU stockroom. Therefore, this sample is representative of a potential source of isocyanate exposure to neonates, since these devices and products in the stockroom, particularly those that were tested, were the ones routinely used during their care/treatment procedures, in some cases for extended time periods and therefore longer exposure times.

Detection of some of the MDI species in the medical devices and products, although low, indicates that further research should be conducted to evaluate the possibility of neonatal skin exposure from contact during their stay in the NICU. This can be done with direct skin exposure assessment methods such as tape stripping followed by analysis of keratin-isocyanate adducts by MS/MS, since isocyanates react instantly with skin components. MDI, one of the most commonly used isocyanates[66] is regarded as one of the leading causes of isocyanate sensitization in the PU/PUF industry.[67] Further testing on biomarkers can use isocyanate albumin immunoglobulin G or E (IgG and IgE) conjugates.

While isocyanate IgE conjugate measurement indicates sensitization, the detection of IgG conjugate may serve as an indication of both exposure (systemic absorption) and sensitization. Additionally, a previous case study has suggested that there is the potential for isocyanate to cause sensitization through dermal exposure to MDI-containing medical devices and products or materials such as exposure to synthetic plaster cast in a health care worker.[68] Therefore, the implication for sensitization or its contribution as a risk factor for childhood asthma should be further evaluated in this population.

Second, the SWYPE™ detector was validated and assessed in previous studies,[33,36] and demonstrated as a highly specific indicator of aliphatic isocyanate on skin (100%) or work surfaces (75%) without interferences from other chemicals. Positive samples are indicators of the presence of isocyanates in and on the surfaces, as well as on the skin.[33] The SWYPE™ is also a specific tool to aid in the identification of aliphatic versus aromatic isocyanate types without cross interference.[33,36] The SWYPE™ provides a useful, quick and relatively inexpensive tool for rapid assessment of isocyanate presence and a crude indicator of the amount, and was used in this study as a guide in selecting the devices and products for further quantitative analysis.

Additionally, our study used well validated analytical methods to quantify the amounts of different isocyanate species that allowed us to know what isocyanates might directly pose a risk of skin exposure to neonates. It helps future studies on isocyanate biomarkers in these infants.

Limitations

This study has several limitations. First, this was a pilot study, not a hypothesis testing study. Therefore, the number of devices and products tested, as well as the numbers of repeated testing, referred to as "Run 1" and "Run 2" in the qualitative assessment were limited (Tables 2 and 3). Moreover, there could be additional devices and products in the inventory stock that may indicate isocyanate presence, at any given range of concentrations that we did not have an opportunity to test as yet. However, although a limited number of medical devices and products were tested in this study, of those tested, the positive results are deemed valid and are promising for expanding our study to include more, as well as other types and species of isocyanates to be measured in future investigations.

Second, although the SWYPE™ is a specific tool to aid in the identification of aliphatic versus aromatic isocyanate types without cross interference,[33,36] this wipe pad relies on a much higher LOD, therefore has lower sensitivity than was observed in this study's quantitative analysis. The earlier validation study[36] showed that the sensitivity was only 55% for surface samples in the laboratory setting. Therefore, a negative sample in our study may not be truly representative as negative, and may contain isocyanates at levels not detectable by the SWYPE™ wipes. Devices and products deemed as negative may contain isocyanates that could be measured using more sensitive quantitative methods.

Third, while the UPLC-MS/MS quantitative analysis employed herein this study is highly sensitive and specific, this method of product testing is labor intensive and expensive. Thus only a limited number of samples were tested in this study.

Moreover, only MDI species were measured in the quantitative analysis due to limited resources. Other isocyanates (TDI and HDI) were not tested, although the analytical methods are now available to test for them in

the same samples. As far as we know, from the qualitative testing, at least the neonatal fluidized position cushions contained aliphatic isocyanates, but we were unable to analyze aliphatic isocyanates.

The potential for selection bias is inescapable in this type of study, because a limited sample from the NICU inventory list (Appendix I) were subjectively selected for testing. In addition, selection of medical devices and products based on their potential or known isocyanate source also lends to the well-known ubiquitous and unavoidable investigator bias. It is not unusual for a researcher to have preconceived ideas about the project that she/he is about going to conduct to "prove" her or his research hypothesis. In this study, some devices and products may have been selected based on the premise that they will be used for longer periods of time in a given subset of the NICU population. One such example is including NICU babies who are usually in the hospital for longer periods of time on the ECMO machine who would have longer contact time with many of the plastic tubing, devices and products.

Although identifying and quantifying the content of isocyanates in medical devices and products is an essential step, this study did not evaluate the actual skin exposures of infants, and their potential risk for sensitization. Studies indicate that isocyanates lead to hypersensitivity reactions,[16] and these hypersensitivity reactions can occur at very low concentrations.[56,57] However, low concentrations of isocyanates that lead to hypersensitivity reactions are technically challenging to monitor.[56]

Regardless, future NICU investigations to evaluate if medical devices and products that contain residual free and/or bound isocyanates would lead to skin exposure should be conducted.

In addition, the original intention to contact most or all of the companies and manufacturers identified on the product inventory list (Appendix I), to assist in further identifying the PU/PUF components in the medical devices and products was unsuccessful, due to proprietary ingredients used in the products and devices, limiting our selection of appropriate devices and products for testing.

Conclusion

This pilot study documents the presence of extractable residual MDI in a number of NICU medical devices and products. Currently, it is not clear if low levels of the detected residual isocyanates are transferrable to, or may be absorbed through the skin. Therefore, it is uncertain if skin exposure to isocyanates occurs in the neonatal population. However, these findings suggest the need to further investigate whether residual isocyanates are transferrable to, and absorbed through neonatal skin. Tailored studies are needed to quantify and characterize skin exposure determinants, assess biomarkers in the blood and urine, and prospectively follow the infants to evaluate sensitization susceptibility, and the development of future asthma. Additionally, quantification of other residual isocyanates (TDI and HDI) in medical devices and products should be assessed, and are currently being planned.

Finally, these findings support the need to adopt a directed and integrated approach to reducing potential residual isocyanate exposures in medical devices and products and direct contact of NICU babies and healthcare workers with them.

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Authors Contributions

GF, YL, DAS, JN and SR designed the study. GF, SA, SR and JN collected the inventory data. GF, SA and YL conducted the qualitative assessment. HH and DB conducted the quantitative measurement. GF, SB and YL conducted the data analysis. GF, DAS and YL drafted the initial manuscript. All authors read, revised and approved the final manuscript.

List of Abbreviations

ECMO: extracorporeal membrane oxygenation
EITC: ethyl isothiocyanate
DETU: diethylthiourea
HDI: hexamethylene diisocyanate
HMW: high molecular weight
HPLC: high performance liquid chromatography
IPDI: isophorone diisocyanate
LMW: low molecular weight
LOD: limit of detection
MAP: 1-(9-anthracenylmethyl)piperazine
MDI: methylene diphenylmethane diisocyanate
MRM: multiple reaction monitoring
NCO: Nitrogen, Carbon, Oxygen
NCS: Nitrogen, Carbon, Sulfur
NICU: neonatal intensive care unit
PUF: polyurethane foam
OSHA: Occupational Safety and Health Administration
SD: standard deviation
SDSs: safety data sheets
TDI: toluene diisocyanate
SRM: Selected reaction monitoring.

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Appendix I. Inventory list of medical devices and products used at a local Medical Center NICU.

NAME OF DEVICE	NAME OF DEVICE
Sorba View 2000 with 2 part Hubguard	Esophogheal Probe, Meas 4400 Series, Temperature probe
Sorba View 200 Ref SV30 NX7	Green Pacifier
BioPatch Protective Disk	Purple Preemie Pacifier
Neonatal Dressing Change Tray	Micro Preemie Pacifier
LNOP SoftTouch NeoPT-L	Medela Special Needs Feeder w/ 80 mL container
NeoLead (Radiolucent)	Therma-Liner TM
Micro NeoLead	Chem Strips Sure Step Pro
Neonatal Pre-Wired Monitoring Electrodes	Glucose High Control Sure Step Pro
Delta- Net Stockinette	Glucose Low Control Sure Step Pro
NeoGrip Multipurpose Tubing & Cable Holders	#1 BP Cuff Allegiance Brand Tactics Soft Blood Pressure Cuff
NeoBar ET Tube Holder N710 (Ultra)	#2 BP Cuff Allegiance Brand Tactics Soft Blood Pressure Cuff
NeoBar ET Tube Holder N712 (Small)	#3 BP Cuff Allegiance Brand Tactics Soft Blood Pressure Cuff
NeoBar ET Tube Holder N713 (Large)	#4 BP Cuff Allegiance Brand Tactics Soft Blood Pressure Cuff
NeoBar ET Tube Holder N715H (Macro)	Dual-Scale Digital Oral Thermometer
NeoBar ET Tube Holder N715F (Macro)	Neo-Term Temperature Sensor
NeoBar ET Tube Holder N714 (XL)	Disposable Skin Temperature Probe
NeoBar ET Tube Holder N716 H (Jumbo)	Infinity Orange Feeding Bag (100 ml Enternal Pump Delivery Set
Neonatal/Pediatric PICC Single Lumen	2 x 2 Gauze Kendal Versalon
Neonatal/Pediatric PICC Double Lumen	Curity Single Tipped Applicators
Hubguard Securement Device	Cotton Tipped Applicators
BD Introsute-N Precision Introducer	Kerlix Antimicrobial Large Roll
Neo Armboard	Petrolatum Gauze Cision Dressing 1 × 8
Cloth Tape 1/2 inch	Dressing Xeroform Petro 9 × 5
Cloth Tape 1 inch	All purpose Sponge 4 × 4
Clear Tape 1/2 inch	All purpose Sponge 3 × 3
Clear Tape 1 inch	All purpose Sponge 2 × 2 with split
Pedicraft Pedi Armboard	Duoderm (Extra Thin) Dressing
Cushion Soft Insta-Putty Silicon Ear Plugs	Aquacel
LL Extension Set	Mepilex Ag w/ Safetac Technology
Slip Tip Extension Set	Tegaderm Film
Tourniquet	Breast Pump Kit
Tegaderm 1.5 x 1.5	Store ′N Pour Breast Milk Storage Bags
Tegaderm Transparent Dressing w/Label	Flexishield Areola Stimulators
24 G IV Cath. w/ Wings	Lanshinoh Cream
24 G IV cath. No Wings	Contact Nipple Shield (small)
Cap Change Kits	Contact nipple shield (xsmall)
Blood Transfer Device–Holder w/ Pre attached Multiple Sample	Z-flo positioner (16 × 24, 20 × 30, 7 × 10)
Multidose Vial	Tongue Depressors-Allegiance
Blue cap Microvalve	Odor Eliminator
Female LL Cap Luer Lock Cap	Wee Specs Phototherapy Mask
Single Dose Alaris Caps	Sterile Glove (6, 6.5, 7, 7.5, 8, 8.5)
Heel Warmers w/Tape	Wash cloth
IV Site Protectors	Baby Soap
IV Site Protectors	Cotton umbilical tape
Smartsite Infusion Set	Arterial blood sample
Baxter Non-DEHP Micro Volume Extension Set	Multipak Non-Adherent Wound Dressing

(*Continued*)

Appendix I. (*Continued*)

NAME OF DEVICE	NAME OF DEVICE
Baxter Extension Set	2.5 Fr/ch (0.8 mm × 12 in) Polyurethane Umbilical vessel catheter with Luer lock hub
PDI Povidone Iodine Prep Pad	3.5 Fr/ch (1.1 mm × 015 in) Polyurethane Umbilical vessel catheter with Luer lock hub
One step Patient preoperative skin preparation	5.0 Fr/ch (1.7 mm × 15 in) Polyurethane Umbilical vessel catheter with Luer lock hub
Detachol Adhesive Remover Latex Free	3.5 F double lumen UVC umbilical CATH, double lumen silicone umbilical catheter
Safety-Lok Blood Collection Set IV admin. 23G IV Cath. 75 Winged	5 French
Safety-Lok Blood Collection Set IV admin. 25G IV Cath. 75 Winged	Fixed cove wire guide straight
Blue/Purple Lancets	Heat Seal Sterilization Pouch 4.5 × 11Ó
Newborn Tenderfoot Gentle heel incision device	Suture removal kit
Micro-Preemie Tenderfoot Gentle heel incision device	Disposable Scalpel
Preemie Tenderfood	O.O. Towel
E swab collection & Transport system	Pampers-Swaddlers
6.5F Feeding Tube Kendall Argyle Indewll Feeding Tube	S2-1 Diapers
10F Repogle Tube Double lumen gastric tube	S2-2 Diapers
8F Repogle Tube Double lumen gastric tube	Newborn
6F Repogle Tube Double lumen gastric tube	Preemie
Lukens Tube Allegiance Polystryrene Aspiration Tube w/Rubber tubing and stopper	Extra-small <800 g
Bulb Syringe, Ear/Ulcer Syringe	Medium 1250 g–2250 g
Blue Repogle Adapter/Catheter Adapter	Beary Small Economical Diapers 22B Large Preemie Size
Red Suction Canister, Tube 18′ w/connectors	Baby Wipes
Pulse Ox probe, Masimo Set	Toothete Disposable oral swabs w/dentifrice Latex free
	Johnson's Baby Shampoo