also suggestive of both subgroups with asthma having lower extracellular IL-26 protein than do healthy volunteers. Similarly, the data sets on IL-26 mRNA in BAL leukocytes, as well as protein in alveolar parenchymal tissue, support the idea that there is more gene expression leading to higher protein production of IL-26 in uncontrolled compared with controlled asthma, and that there is less IL-26 protein in the peripheral airways of adult patients with asthma than in healthy volunteers.

Although the ACT score represents a continuous variable rather than a threshold one, this score can be a clinically useful indicator of disease control with a borderline value of 20 as the established "divider" between uncontrolled and controlled asthma.[1-3] Given this fact, our findings in the group defined as having uncontrolled asthma, including poorly controlled and uncontrolled disease, are intriguing. Here, we obtained evidence that, in uncontrolled asthma, low extracellular IL-26 protein signifies patients with an even poorer disease control. Possibly, these patients are unable to respond with enhanced local IL-26 protein, a response that may thus be both reactive and protective. The finding of a negative correlation between IL-26 protein in cell-free BAL fluid and FEV_1 (% predicted) in the pooled group of all patients with asthma is also compatible with a reactive and protective cytokine response in terms of extracellular IL-26. Along these lines, the negative correlation between IL-26 protein in cell-free BAL fluid and lymphocytes, and eosinophils, in BAL samples from patients with uncontrolled asthma is suggestive of a reactive mechanism that serves to protect from excessive mobilization of key luminal leukocytes as well. The clear and positive correlation between IL-26 mRNA in BAL cells and F_ENO_{50} in all groups of patients with asthma is also suggestive of a reactive and protective role for IL-26.

Even though both IL-26 mRNA in BAL cells and IL-26 protein in cell-free BAL fluid did display a higher median level in uncontrolled than in controlled asthma, there was no positive correlation between these 2 outcomes in patients or in healthy volunteers. We think that this can be explained as follows: Extracellular IL-26 protein in BAL samples reflects the production and release from several cellular sources, including structural cells such as bronchial epithelial cells and lung fibroblasts, as well as leukocytes.[4,8,9] In contrast, the IL-26 mRNA that we quantified to assess gene expression is likely to originate exclusively from luminal leukocytes in the airways.

Similarly for the case for extracellular IL-26 protein, we obtained evidence for a negative correlation between gene expression for IL-26 in airway leukocytes and counts for total leukocytes and lymphocytes in uncontrolled asthma. In the same subgroup, there was also a negative correlation for this gene expression and counts for neutrophils and macrophages. For neutrophils, this may seem paradoxical, because extracellular IL-26 and IL-8 protein do correlate in a positive manner in the pooled group of all patients with asthma, with indicated trends in the subgroups. We suspect that this finding relates to the fact that IL-26 can exert both pro- and anti-inflammatory actions in terms of release of the very same neutrophil-mobilizing cytokines, depending on the cellular target.[4]

With the exception of 3 patients with controlled asthma, all patients had treatment with a narrow range of low to moderate doses of ICSs. This fact makes it impossible to determine the role of ICSs with respect to the difference in local IL-26 production between uncontrolled and controlled asthma. However, we recently demonstrated that treatment with a glucocorticoid effectively inhibits the release of IL-26 protein in human lung fibroblasts *in vitro*.[9] Thus, from a hypothetical point of view, ICSs may account for the average decrease in extracellular IL-26 protein that we observed in the pooled group of all patients with asthma.

Ellen Tufvesson, PhD[a]
Prajakta Jogdand, PhD[b]
Karlhans Fru Che, PhD[c]
Bettina Levänen, PhD[c]
Jonas S. Erjefält, PhD[b]
Leif Bjermer, MD, PhD[a]
Anders Lindén, MD, PhD[c,d]

From [a]the Department of Clinical Sciences Lund, Respiratory Medicine and Allergology, Lund University, Lund, [b]Airway Inflammation, Department of Experimental Medical Science, Lund University, Lund, [c]the Unit for Lung and Airway Research, Institute of Environmental Medicine, Karolinska Institutet, Stockholm, and [d]the Department of Respiratory Medicine and Allergy, Karolinska University Hospital Solna, Stockholm, Sweden. E-mail: anders.linden@ki.se.

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Exposure to breast milk triclosan and parabens and eczema phenotypes at 12 months: A nested case-control study

To the Editor:

Although breast-feeding has a range of health benefits, the association between breast-feeding and eczema reported between studies has been inconsistent.[1] The variability in associations

TABLE I. Unadjusted associations* between triclosan or parabens and eczema and atopy outcomes at age 1 year

		No atopy and no eczema	Atopy (no eczema)		Nonatopic eczema		Atopic eczema	
Molecule	N	Proportion exposed	Proportion exposed	OR (95% CI)	Proportion exposed	OR (95% CI)	Prevalence	OR (95% CI)
Triclosan	60	46.7%	40.0%	0.77 (0.14-4.05)	40.0%	0.77 (0.14-4.05)	33.3%	0.58 (0.10-3.13)
Methyl-paraben	60	66.7%	46.7%	0.45 (0.08-2.38)	73.3%	1.36 (0.22-9.01)	100.0%	**8.83 (1.07-∞)**
Propyl-paraben	60	26.7%	33.3%	1.36 (0.22-9.00)	53.3%	3.02 (0.55-19.54)	46.7%	2.34 (0.42-15.02)
Butyl-paraben	60	0.0%	20.0%	4.32 (0.43-∞)	20.0%	4.32 (0.43-∞)	53.3%	**19.73 (2.58-∞)**

Estimates in boldface have $P < .05$.
*Associations estimated using exact logistic regression. The no atopy and no eczema group was used as the comparison group for all analyses.

TABLE II. Adjusted associations* between triclosan or parabens and eczema and atopy outcomes at age 1 year

			Atopy (no eczema)	Nonatopic eczema	Atopic eczema
Molecule	N	No atopy and no eczema	aOR (95% CI)	aOR (95% CI)	aOR (95% CI)
Triclosan†	60	1	0.92 (0.14-5.94)	0.66 (0.09-4.07)	0.72 (0.13-3.98)
Methyl-paraben‡	60	1	0.55 (0.09-3.20)	1.02 (0.14-7.08)	6.07 (0.70-∞)
Propyl-paraben§	60	1	1.41 (0.22-9.59)	2.99 (0.53-20.31)	2.25 (0.40-14.23)
Butyl-paraben‖	60	1	2.83 (0.26-∞)	3.72 (0.37-∞)	**10.6 (1.36-∞)**

Estimates in boldface have $P < .05$.
aOR, Adjusted odds ratio.
*Associations estimated using exact logistic regression. The no atopy and no eczema group was used as the comparison group for all analyses.
†Adjusted for maternal smoking, age, and education level.
‡Adjusted for maternal and paternal eczema.
§Adjusted for maternal age.
‖Adjusted for maternal and paternal smoking, older sibling(s), and maternal eczema.

between breast-feeding and eczema may be due to breast milk containing a wide range, and variable levels, of immunologically active substances, and potentially transmitting toxic substances, such as the antimicrobial agents triclosan and parabens, from mother to infant.[2] These agents are used in a range of foods and medications, but the primary source of exposure is through personal care products.[3] Because of ongoing consumer concerns with their safety, there are a growing number of "paraben-free" products becoming available. Exposure to these substances through breast milk may inhibit the establishment of a healthy gut microbiome and have an impact on the child's risk of developing allergic diseases. Alternatively, these compounds may promote proinflammatory responses, including production of thymic stromal lymphopoietin, or induce epigenetic changes, such as altered methylation profiles.[4]

To assess whether levels of breast milk triclosan and parabens were associated with eczema and sensitization outcomes, we conducted a nested case-control study within the Melbourne Atopy Cohort Study participants, all of whom have a family history of asthma or allergic disease. We selected 60 children with a 3-month breast milk sample (for demographic details, see Table E1 in this article's Online Repository at www.jacionline.org), grouped on the basis of their sensitization and eczema status at 12 months. We selected 15 participants each with (a) neither, (b) atopy only (no eczema), (c) nonatopic eczema, or (d) atopic eczema (both eczema and sensitization). Sensitization was defined as a positive skin prick test (2 mm or greater wheal) result to 1 or more of 6 allergens. Eczema was defined by either a parent report of a doctor diagnosis of "eczema" or use of topical steroids for a rash excluding the nappy area. A gas chromatograph coupled with a tandem mass spectrometer was used to measure triclosan and 6 parabens (for further details, see Table E2 and Online Repository in this article's Online Repository at www.jacionline.org). Because of small counts, exact logistic regression models were used, with "no atopy and no eczema" as the comparison group for all analyses. Associations were adjusted for the following factors if they had some association ($P < .1$) with the specific contaminant: parental age, history of smoking or eczema, maternal tertiary degree, socioeconomic status based on father's occupation, presence of older siblings, and sex.

Because the concentrations were above the limit of detection in 5% or less of samples, isobutyl-, isopropyl-, and ethyl-paraben were excluded from the analyses (see Table E3 in this article's Online Repository at www.jacionline.org). Triclosan, methyl-, propyl-, and butyl-paraben were included, and concentrations of methyl- and propyl-paraben in breast milk were weakly correlated (see Table E4 in this article's Online Repository at www.jacionline.org).

In unadjusted analyses, detectable levels of methyl- and butyl-paraben in breast milk were associated with increased risk of atopic eczema (Table I). Adjustment for baseline factors reduced the strength of these associations, and only detectable levels of butyl-paraben were associated with increased risk of atopic eczema in the adjusted model (Table II). Adjustment for maternal or paternal asthma or allergic rhinitis, or maternal atopy (defined as any positive [≥3 mm wheal] to 6 allergens tested on skin prick test during the first 2 years of child's life), did not materially alter the association between butyl-paraben and increased risk of atopic eczema. Similar associations were seen if atopic and nonatopic eczema groups were combined and compared with the noneczema groups (see Table E5 in this article's Online Repository at www.jacionline.org).

Few studies have previously examined the associations between parabens or triclosan exposure and allergic disease outcomes. The results from the present study are difficult to compare directly with previous findings, because previous studies have used maternal urine levels, rather than breast milk. Although there are correlations between breast milk, urine, and even amniotic fluid levels of parabens, these associations are not strong. Because of the short half-life (hours) of these compounds, levels will vary dramatically over time. Cross-sectional analyses in older children have supported associations between levels of triclosan, methyl-, propyl-, and butyl-paraben in biological samples and increased risk of aeroallergen sensitization and asthma/wheeze,[5,6] and increased risk of emergency department presentations for asthma (in boys).[7]

Only 2 recently published longitudinal studies have been reported. Lee-Sarwar et al[8] found no overall associations between triclosan levels in maternal plasma during pregnancy and sensitization or wheeze in children up to age 3 years. However, boys whose mothers had higher paraben exposures possibly had increased risk of sensitization, a result not seen in girls. No eczema outcomes were examined in this study. Berger et al[9] observed that increasing levels of propyl-paraben in maternal urine collected during pregnancy were weakly associated with a reduction in probable asthma at age 7 years, whereas no associations were seen with aeroallergen sensitization, eczema, or lung function outcomes. There was some evidence that higher levels of methyl-paraben were associated with reduction in both T_H1 and T_H2 cells (estimated using total $CD4^+$ cells as the denominator) in whole blood.[9] Unfortunately, neither study reported associations with butyl-paraben because of 20% to 30% of samples being below the limit of detection.[8,9] In fact, although other studies have measured levels of butyl-paraben, no previous study has reported on associations between butyl-paraben and allergic disease outcomes, because of some participants having levels below the limit of detection.[8,9]

Presence of parabens in breast milk may be acting as a marker of another underlying cause of eczema in the child. Parabens are used as antimicrobial agents in some topical creams, including topical steroids used to treat eczema, and they are also used in medication suspensions (paracetamol and some antibiotics). Having a mother with active eczema or infection during lactation may influence the risk of both having detectable levels of parabens in breast milk and that the infant will develop eczema. Although we adjusted for maternal history of ever having eczema, and this did not materially alter the association (addition or removal of maternal eczema shifted the odds ratio from 10.6 to 12.5 with wide CIs), we did not have data on active maternal eczema or infection during lactation. The concentrations of parabens and triclosan observed in breast milk in this study were very low, and may not have been sufficient to induce alterations in the infant gut microbiome. It remains possible that their presence in breast milk is a marker of other exposure routes (direct exposure of the infant to the products inducing the levels identified in the mother's breast milk), or the effects seen here could be due to impacts on the immune response potentially via epigenetic changes.[4] We were also unable to assess associations with specific IgE or severity of eczema, because these data were not collected. In conclusion, although the observed association between the presence of butyl-paraben in breast milk and increased risk of atopic eczema is plausible, these findings are preliminary due to the limited sample size and should be replicated in future studies.

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Adrian J. Lowe, PhD[a,b]
Xianyu Wang, PhD[c]
Jochen F. Mueller, PhD[c]
Michael J. Abramson, PhD[d]
Ruby Y. Yeh, BEnvSc (Hons)[c]
Bircan Erbas, PhD[e]
Shyamali C. Dharmage, MD, PhD[a,b]*
Caroline J. Lodge, PhD[a,b]*

From [a]the Allergy and Lung Health Unit, Melbourne School of Population and Global Health, University of Melbourne, Parkville; [b]Murdoch Children's Research Institute, Royal Children's Hospital, Melbourne, Victoria; [c]Queensland Alliance for Environmental Health Sciences, The University of Queensland, Woolloongabba, Queensland; [d]the School of Public Health & Preventive Medicine, Monash University, Melbourne; and [e]the School of Psychology and Public Health, La Trobe University, Bundoora, Victoria, Australia. E-mail: lowea@unimelb.edu.au.

*Equal senior author.

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METHODS

Participant recruitment and ethical approval

Expectant mothers were approached during antenatal care visits at the former Mercy Hospital for Women (East Melbourne, Australia) and other private consulting suites.[E1] Children with a parent or older sibling with a history of allergic disease (asthma, eczema, allergic rhinitis, or severe food allergy) were eligible for enrollment. Infants were born between 1990 and 1994. Parents provided informed consent, and the Mercy Hospital Human Ethics Committee granted ethical approval.

Outcome definitions

Sensitization was defined as a positive skin prick test (2 mm or greater wheal) result to 1 or more of 6 allergens.[E1] A 2-mm wheal was used, because in infants, the reactions on skin prick test are generally smaller. Eczema was defined by either a parent report of a doctor diagnosis of "eczema" or use of topical steroids for a rash excluding the nappy area.[E1]

Analytical method

Triclosan and parabens. One milliliter of breast milk samples was thawed at room temperature and spiked with 50 μL of internal standard for quantification purposes. The samples were subsequently extracted by 2 mL of acetonitrile (ACN) and centrifuged at 4000*g* at 4°C for 10 minutes. The supernatants were then transferred and filtered using a 0.2-μm polytetrafluoroethylene filter. The filtrates were subsequently evaporated to near dryness and reconstituted into 10 mL of MilliQ water at pH 4. Subsequently, samples went through solid-phase extraction using HLB cartridges (3 cc), which was preconditioned with 1 mL of ACN and 1 mL of MilliQ water at pH 4. Samples were then loaded on the cartridges followed by washing with 1 mL of 5% ACN in MilliQ water at pH 4 solution. Cartridges were then dried for 3 minutes under vacuum before being eluted with 2 mL of ACN. The extracts were subsequently evaporated to approximately 25 μL and derivatized using 70 μL of bis(trimethylsilyl)trifluoroacetamide containing 1% trimethylchlorosilane. The samples were then evaporated under a gentle nitrogen stream to near dryness before being reconstituted into 50 μL of isooctane before instrument analysis. Samples were analyzed using a TRACE GC Ultra coupled to a TSQ Quantum XLS triple quadrupole mass spectrometer equipped with a TriPlus Autosampler.

Statistical methods and measurement of possible confounding factors

A number of factors were considered as potential confounding factors in the statistical models. Socioeconomic status, based on father's occupation, was coded using the ANU-3.[E2] Correlations between specific breast milk contaminants were estimated using Spearman correlation coefficients to account for samples with nondetectable levels. Correlations with P less than .05 were considered significant.

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TABLE E1. Baseline characteristics of sample

Characteristic	Proportion (n/N)	Mean ± SD or median (IQR)	Range
Female sex	50.0% (30/60)		
First born child	50.0% (30/60)		
Maternal eczema ever	45.0% (27/60)		
Paternal eczema ever	28.3% (17/60)		
Paternal smoking (ever)	43.3% (26/60)		
Maternal smoking (ever)	35.0% (21/60)		
Maternal completion of tertiary education	71.7% (43/60)		
Father's occupation status (ANU-3 scale[E2]), mean ± SD		44.8 ± 21.1	0-91.9
Maternal age (y), mean ± SD		31.2 ± 4.6	23-40
Paternal age (y), mean ± SD		32.9 ± 5.3	24-48
Weeks of breast-feeding, median (IQR)		46 (31-64)	10-104
Weeks of exclusive breast-feeding, median (IQR)		18 (11-22)	1-29

IQR, Interquartile range.

TABLE E2. List of target compounds and corresponding internal standards

Target compounds	Internal standard
Triclosan	$^{13}C_{12}$-triclosan
Methyl-paraben	$^{13}C_6$-methyl-paraben
Ethyl-paraben	$^{13}C_6$-ethyl-paraben
Isopropyl-paraben	$^{13}C_6$-propyl-paraben
Propyl-paraben	$^{13}C_6$-propyl-paraben
Butyl-paraben	$^{13}C_6$-propyl-paraben
Isobutyl-paraben	$^{13}C_6$-propyl-paraben

TABLE E3. Distributions of molecules assessed in breast milk and parameterization of exposure

Molecule	Tested	Limit of detection (ng/mL)	% detectable	Minimum-maximum
Triclosan	60	0.072	40.0%*	0.08-23.1
Parabens				
Methyl-paraben	60	0.030	71.7%*	0.06-17.8
Propyl-paraben	60	0.042	40.0%*	0.044-.47
Butyl-paraben	60	0.022	23.3%*	0.023-0.57
Isopropyl-paraben	60	0.49	1.7%†	4.80
Ethyl-paraben	60	1.6	1.7%†	1.96
Isobutyl-paraben	60	1.4	0%†	—

*Analyzed as detected versus not detected.
†Excluded from statistical analyses.

TABLE E4. Spearman correlation* matrix between concentrations of triclosan and assessed parabens†

Molecule	Triclosan	Methyl-paraben	Propyl-paraben	Butyl-paraben
Triclosan	1			
Methyl-paraben	0.09 (−0.18 to 0.36)	1		
Propyl-paraben	−0.06 (−0.26 to 0.19)	**0.34 (0.09 to 0.58)**	1	
Butyl-paraben	0.09 (−0.15 to 0.34)	0.19 (−0.06 to 0.43)	0.05 (−0.19 to 0.31)	1

Correlations with $P < .05$ are in boldface.
LOD, Limit of detection.
*95% CIs estimated using bootstrap techniques.
†Samples below the LOD were assigned the value of half of the LOD.

TABLE E5. Unadjusted and adjusted between triclosan or parabens and eczema at age 1 year (regardless of sensitization)

		Proportion exposed		Crude	Adjusted
Molecule	**N**	**No eczema (n = 30)**	**Eczema (n = 30)**	**OR (95% CI)**	**OR (95% CI)**
Triclosan*	60	43.3%	36.7%	0.76 (0.27-2.13)	0.83 (0.27-2.55)
Methyl-paraben†	60	56.7%	86.7%	**4.97 (1.39-17.8)**	3.69 (0.97-14.0)
Propyl-paraben‡	60	33.3%	50.0%	2.00 (0.70-5.68)	1.94 (0.67-5.65)
Butyl-paraben§	60	10.0%	36.7%	**5.21 (1.28-21.2)**	**11.76 (1.85-74.9)**

Estimates in boldface have $P < .05$.
*Adjusted for maternal smoking, age, and education level.
†Adjusted for maternal and paternal eczema.
‡Adjusted for maternal age.
§Adjusted for maternal and paternal smoking, older sibling(s), and maternal eczema.