Elevation of Circulating Th17/Th22 Cells Exposed to Low-Level Formaldehyde and Its Relevance to Formaldehyde-Induced Occupational Allergic Contact Dermatitis

Weihua Mai, MD, Xingwei Liu, MS, Guangxiao Su, MS, Wenying Zhou, BS
Ziping Wen, MS, and Dongqing Lu, MD

Objectives: The aim of this study was to investigate the effects of formaldehyde exposure on Th17 and Th22 cells and its relevance to human occupational allergic contact dermatitis (OACD). **Methods:** Circulating IL17-/IL22-secreting cells and serum IL17/IL22 levels in formaldehyde-exposed workers at Occupational Exposure Limit and nonexposed controls were assessed. **Results:** The $IL17^+$ and $IL22^+$ cell population were detected in both $CD3^+CD8^-$ and $CD3^+CD8^+$ cells. The percentages of circulating $IL17^+$ and $IL22^+$ T cells in the workers with and without ACD history were all elevated, which were more remarkable in the ones with ACD history. Serum levels of IL17 and IL22 between the workers and controls were not significantly different. **Conclusions:** Low-level formaldehyde exposure may increase circulating IL17-/IL22-producing T cells ($CD8^-$ and $CD8^+$), possibly involved in the development of human OACD. But it may not alter serum levels of IL17/IL22 before the appearance of OACD symptoms.

Occupational skin diseases (OSDs) are the most common nontraumatic occupational illnesses in many countries, with serious health effects on hazard-exposed workers, resulting in severe economic losses and social problems.[1] Therefore, it is quite essential to prevent and control OSDs effectively. The goal of the US Public Health Service for the year 2010 was to reduce national OSDs to an incidence of no more than 46 per 100,000 full-time workers.[2]

Occupational allergic contact dermatitis (OACD) is one of the most prevalent OSDs,[1,2] with a prevalence of 15% to 25%.[3] It is a type IV, delayed-type hypersensitivity response to xenobiotics or haptens in contact with the skin. The most common allergens in occupational exposure include metals (such as nickel), fragrance, rubber, organic solvents, preservatives, and so on. Formaldehyde, a widely used organic compound in manufacturing, health care, and embalming,[4] is a well-known OACD inducer.[5,6]

Patch-test is an important diagnostic tool for the assessment of ACD.[7] A series of allergens are applied to the patients, and evaluated in 24, 48, and 72 hours after application. But false-positive reactions may occur when the patient has generalized dermatitis or primary irritants are used, and negative tests may be misleading for various reasons.[8] Systemic symptoms related patch-test were reported in rare cases.[9,10] Therefore, if a more convenient, accurate, and safe method for OACD susceptibility screening could be found, it will be of great value for the prevention and control of OACD.

ACD was considered as a Th1/Th2 imbalance with Th1-predominance for a long period. Recently, it has been suggested that Th17 and Th22 cytokines (IL17 and IL22) are implicated in the development of ACD,[11–14] and unique pathways are preferentially activated by different allergens.[15] Both L17 and IL22 are important for the pathogenesis of ACD, but differ in their functions. IL17 is more involved in the inflammatory response, whereas IL22 seems to have a more protective/regenerative quality.[13,16,17] However, up to now, there are only few data concerning the associations of Th17 and Th22 cytokines with OACD induced by occupational hazards. It was observed that the inflamed skin of nickel-challenged allergic individuals contained infiltrating neutrophils and cells expressing IL17/IL22, suggesting the involvement of IL17 and IL22 in nickel-induced ACD.[18,19] Previous studies were conducted to clarify the possible effects of formaldehyde exposure on the immune system, mainly limited to effects on Th1 and Th2 cells.[20–23] But less is known about the effects of formaldehyde exposure on Th17 and Th22 cells. It was observed that independent formaldehyde exposure at a low concentration (0.2 ppm) increased the skin mRNA expressions of IL17E in NC/Nga mice, even though it failed to induce atopic dermatitis-like skin inflammation.[24] But the effect of formaldehyde exposure on Th17/Th22 cells in exposed workers and its relevance to human OACD remain unclear.

According to Occupational Exposure Limit (OEL) by Scientific Committee for Occupational Exposure Limits (SCOEL) 2008,[25] it was supposed that an 8-hour time-weighted average exposure to 0.2 ppm formaldehyde with a short-term exposure limit of 0.4 ppm would be not irritating or genotoxic in humans. Nevertheless, even under low-level formaldehyde exposure at OEL, a minority of exposed workers develop OACD. In order to investigate the effects of formaldehyde exposure on Th17 and Th22 cells and evaluate the participation of these cells in human OACD, we conducted studies to explore the alterations of circulating IL17-/IL22-secreting cells and IL17/IL22 levels in the workers exposed to formaldehyde at proposed OEL. We supposed that low-level formaldehyde exposure may alter IL17-/IL22-secreting cells and L17/IL22 levels before the appearance of skin lesions, involved in the development of OACD. If future studies will show that the workers with elevated IL17-/IL22-secreting T cells and L17/IL22 levels develop formaldehyde-induced OACD in the future, then Th17/Th22 cells could be used as indicators for future OACD.

METHODS

Subjects

A total of 104 workers exposed to low-level formaldehyde at proposed OEL (0.2 ppm), and 90 nonexposed controls with no history of formaldehyde or other chemicals exposure, were enrolled. All subjects, matched for sex and age, were selected from the individuals who took occupational or common health examinations

From the Department of Prevention and Healthcare, the Fifth Affiliated Hospital of Sun Yat-sen University, Zhuhai, Guangdong Province, China (Dr Mai, Su); Department of General Surgery, the Fifth Affiliated Hospital of Sun Yat-sen University, Zhuhai, Guangdong Province, China (Mr Liu); Department of Laboratory Science, the Fifth Affiliated Hospital of Sun Yat-sen University, Zhuhai, Guangdong Province, China (Ms Zhou); and Department of Dermatology, the Fifth Affiliated Hospital of Sun Yat-sen University, Zhuhai, Guangdong Province, China (Mr Wen, Mr Lu).

This work was supported by Science and Technology Planning Project of Zhuhai city, China (Grant No: 2014D0401990013) and Natural Science Foundation of Guangdong Province, China (Grant No: 2014A030313028).

The authors have no competing interests.

Address correspondence to: Weihua Mai, MD, Department of Prevention and Healthcare, the Fifth Affiliated Hospital of Sun Yat-sen University, No. 52 East Meihua Road, Zhuhai, Guangdong Province 519000, China (weihuamai2004@163.com).

DOI: 10.1097/JOM.0000000000001074

TABLE 1. Demographics of Formaldehyde-exposed Workers and Nonexposed Controls

Groups	Male (*n*)	Female (*n*)	Age, years	Exposure Duration to Formaldehyde, years	With Cigarette History (*n*)	With Alcohol History (*n*)
Formaldehyde-exposed workers	96 (92.3%)	8 (7.7%)	39.85 ± 1.134; (95% CI: 37.51∼42.18)	8.68 ± 3.975 (4∼20)	48	24
Nonexposed controls	80 (88.9%)	10 (11.1%)	40.67 ± 2.768; (95% CI: 34.73∼46.60)	0	40	18
P	0.820		0.166		0.866	0.714

95% CI, 95% confidence interval.

in the Fifth Affiliated Hospital of Sun Yat-sen University from June 2015 to October 2016. Demographics of the workers and controls are summarized in Table 1. Nineteen exposed workers had a clinical history of ACD. None of the workers and controls had other inflammatory/autoimmune diseases or received immunosuppressant/glucocorticoid treatment in the previous 3 months. The concentrations of formaldehyde in workplaces were assessed by the qualified agencies. Blood samples were obtained from all subjects with informed consent. The eosinophil counts in peripheral blood were assessed in Clinical Laboratory of the hospital. The study was approved by the Local Ethical Committee of the Fifth Affiliated Hospital of Sun Yat-sen University.

Flow-Cytometric Analysis

As CD4 expression on T cells was downregulated during culture with phorbol 12-myristate 13-acetate (PMA)/Ionomycin and brefeldin A (BFA)/Monensin, $CD3^+CD8^+$ and $CD3^+CD8^-$ cells intracytoplasmic positive for IL17 and IL22 were assessed instead. First, to evaluate the activation of T cells, 125 μL fresh heparinized blood was incubated in 125 μL RPMI 1640 medium (Gibco, ThermoFisher Scientific, Waltham, MA) containing L-Glutamine, stimulated with 1 μL PMA/Ionomycin Mixture (PMA12.5 μg/mL, Ionomycin 0.25 mg/mL, dissolved in ethanol, 250 × ; Multisciences Biotech, Hangzhou, Zhejiang, China) for 6 hours at 37°C. After incubation, 50 μL cells were stained with 5 μL ECD-conjugated anti-CD3 and PE-conjugated anti-CD69 mAbs (Beckman Coulter, Indianapolis, IN) for 15 minutes at room temperature. Then, 300 μL OptiLyse C (Beckman Coulter, Indianapolis, IN) was added, incubated for 20 minutes to lyse the remaining erythrocytes. After wash, cell labelings were analyzed on Epics XL-MCL flow cytometer (Beckman Coulter, Indianapolis, IN). Only when the proportion of activated T cells ($CD3^+CD69^+$) was more than 90%, the following procedures were conducted.

Next, 125 μL fresh heparinized blood was incubated in 125 μL RPMI 1640 medium containing L-Glutamine, stimulated with 1 μL PMA/Ionomycin mixture, in the presence of 1 μL BFA/Monensin mixture (BFA 0.75 mg/mL, Monensin 0.35 mg/mL, dissolved in ethanol, 250 × ; Multisciences Biotech, Hangzhou, Zhejiang, China) for 6 hours at 37°C. After incubation, 120 μL cells were directly stained with 5 μL ECD-conjugated anti-CD3 and PC5-conjugated anti-CD8 mAbs (Beckman Coulter, Indianapolis, IN) for 15 minutes. Then, cells were fixed with 100 μL fixation agent (Formaldehyde, IntraPrep; Beckman Coulter, Indianapolis, IN) for 15 minutes in the dark. After wash, cells were permeabilized with 100 μL permeability agent (Saponine, IntraPrep; Beckman Coulter, Indianapolis, IN), and the remaining erythrocytes were lysed. Finally, cells were stained with 5 μL PE-conjugated anti-IL17A mAb (50 μg/mL; eBioscience, Affymetrix, Waltham, MA) and 5 μL fluorescein isothiocyanate-conjugated anti-IL22 mAb (25 μg/mL; eBioscience, Affymetrix, Waltham, MA) for 30 minutes, using 5 μL PE-labeled and fluorescein isothiocyanate-labeled mouse IgG1 mAbs (100 μg/mL: eBioscience, Affymetrix, Waltham, MA) as Isotype Controls. After wash, fluorescence profiles were acquired on Epics XL-MCL flow cytometer and the data were analyzed with Expo32-ADC Analysis software (Beckman Coulter, Indianapolis, IN).

ELISA

Serum concentrations of IL17 and IL22 were assessed with commercially available sandwich ELISA kits: IL17 and IL22 Quantikine kits (R&D Systems, Bio-Techne, Minneapolis, MN), according to the manufacturer's instructions. Microplate reader (iMark; Bio-Rad, Hercules, CA) was used to measure the absorbance at 450 nm.

Statistical Analysis

On the basis of the normal distribution of data tested by the Kolmogorov–Smirnov, differences of T cell subsets, IL17-/IL22-producing T cells, and serum levels of IL17/IL22 among groups were compared by the one-way analysis of variance (ANOVA). And pairwise comparisons were tested by least significant difference (LSD). The differences of sex, cigarette, and alcohol history between groups were compared by crosstabs Chi-square tests (Pearson Chi-square or Continuity Correction). An analysis of bivariance correlations was used to estimate the correlations. Missing data were not included in the statistics. All statistical procedures were performed using the statistical package of the social sciences 16.0 (SPSS16.0) and *P* value less than 0.05 was considered to be significant.

RESULTS

Alternations of T Cell Subsets in Formaldehyde-Exposed Workers

Compared with the controls, the percentages of peripheral $CD3^+CD8^-$ cells in the workers with and without ACD history were both elevated (68.79 ± 2.916 vs 48.61 ± 2.498, $P = 0.000 < 0.05$; 55.87 ± 2.158 vs 48.61 ± 2.498, $P = 0.029 < 0.05$), whereas the proportions of $CD3^+CD8^+$ cells were declined (30.86 ± 2.960 vs 51.39 ± 2.498, $P = 0.000 < 0.05$; 44.13 ± 2.158 vs 51.39 ± 2.498, $P = 0.029 < 0.05$). The alternations of $CD3^+CD8^-$ and $CD3^+CD8^+$ cells in the workers with ACD history were more obvious, than the ones without ACD history (68.79 ± 2.916 vs 55.87 ± 2.158, $P = 0.003 < 0.05$; 30.86 ± 2.960 vs 44.13 ± 2.158, $P = 0.003 < 0.05$).

Elevation of IL17-/IL22-Producing T Cells in Formaldehyde-Exposed Workers

The proportions of $CD3^+CD69^+$ cells in 102 exposed workers and 86 controls were more than 90% ($99.26 \pm 0.556\%$), indicating that the majority of T cells in these subjects were activated. Representative profiles of $CD3^+CD69^+$ cells from the workers and controls are shown in Fig. 1.

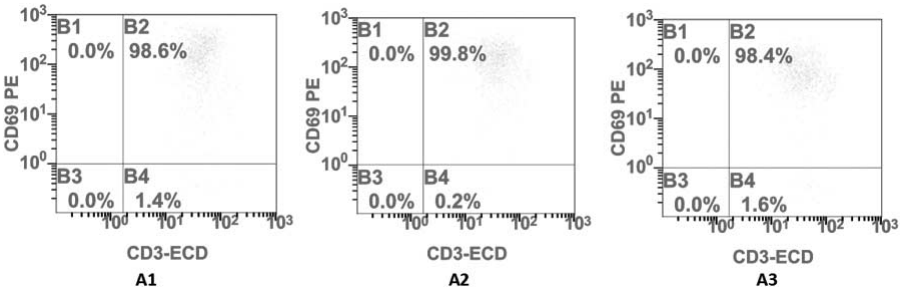

FIGURE 1. Representative profiles of circulating activated T cells ($CD3^+CD69^+$) in formaldehyde-exposed workers and nonexposed controls. After activated by PMA/Ionomycin mixture, the activation of T cells was evaluated. The upper right quadrant represented the percentage of activated T cells ($CD3^+CD69^+$), which was more than 90% in formaldehyde-exposed workers with ACD history (A1), formaldehyde-exposed workers without ACD history (A2), and nonexposed controls (A3), respectively.

A discernible population of $CD3^+CD8^-IL17^+$ and $CD3^+CD8^-IL22^+$ cells were detected in peripheral blood. Compared with the controls, the percentages of circulating $CD3^+CD8^-IL17^+$ and $CD3^+CD8^-IL22^+$ cells from the workers with and without ACD history were elevated ($CD3^+CD8^-IL17^+$cells: $5.53 \pm 0.366\%$ vs $1.92 \pm 0.236\%$, $P = 0.000 < 0.05$; $2.80 \pm 0.288\%$ vs $1.92 \pm 0.236\%$, $P = 0.025 < 0.05$. $CD3^+CD8^-IL22^+$cells: $3.56 \pm .275\%$ vs $0.64 \pm .0.081\%$, $P = 0.000 < 0.05$; $1.36 \pm .0.121\%$ vs $0.64 \pm 0.081\%$, $P = 0.000 < 0.05$). And the elevations in the workers with ACD history were more remarkable, than the ones without ACD history ($5.53 \pm 0.366\%$ vs $2.80 \pm 0.288\%$, $P = 0.000 < 0.05$; $3.56 \pm .0.275\%$ vs $1.36 \pm 0.121\%$, $P = 0.000 < 0.05$).

Interestingly, $CD3^+CD8^+IL17^+$ and $CD3^+CD8^+IL22^+$ cells were also detected in spite of small amounts. Similarly, the proportions of $CD3^+CD8^+IL22^+$ cells in the workers with and without ACD history were higher than the controls ($0.86 \pm 0.072\%$ vs $0.15 \pm 0.024\%$, $P = 0.000 < 0.05$; $0.42 \pm 0.043\%$ vs $0.15 \pm 0.024\%$, $P = 0.000 < 0.05$). And the elevation in the workers with ACD history was more obvious, than the ones without ACD history ($0.86 \pm 0.072\%$ vs $0.42 \pm 0.043\%$, $P = 0.000 < 0.05$). The proportion of $CD3^+CD8^+IL17^+$ cells in the workers with ACD history was also enhanced, compared with the workers without ACD history and the controls ($0.99 \pm 0.130\%$ vs $0.62 \pm 0.105\%$, $P = 0.042 < 0.05$; $0.99 \pm 0.130\%$ vs $0.37 \pm 0.796\%$, $P = 0.002 < 0.05$). But it was not significantly different between the workers without ACD history and the controls ($0.62 \pm 0.105\%$ vs $0.37 \pm 0.796\%$, $P = 0.074 > 0.05$). The data are shown in Figs. 2 and 3.

NO Distinct Serum Levels of IL17/IL22 Between Formaldehyde-Exposed Workers and Nonexposed Controls

Serum IL17 levels in all subjects were detected successfully, but the serum levels of IL22 in three workers and two controls were too low to be detected. Serum concentrations of IL17 and IL22 in the workers with and without ACD history seemed a bit higher than the controls, but with no significant differences (IL17: 8.92 ± 1.953 vs 7.40 ± 1.451 pg/mL, $P = 0.580 > 0.05$; 8.22 ± 0.991 vs 7.40 ± 1.451 pg/mL, $P = 0.800 > 0.05$. IL22: 6.79 ± 1.289 vs 5.65 ± 1.310 pg/mL, $P = 0.654 > 0.05$; 5.84 ± 1.015 vs 5.65 ± 1.310 pg/mL, $P = 0.711 > 0.05$). There was no significant difference between the workers with and without ACD history either (8.92 ± 1.953 vs 8.22 ± 0.991 pg/mL, $P = 0.647 > 0.05$; 6.79 ± 1.289 vs 5.84 ± 1.015 pg/mL, $P = 0.908 > 0.05$).

Correlation Between IL17-/IL22-Producing T Cells and the Eosinophil Counts

There were positive correlations between the proportions of $CD3^+CD8^-IL17^+$ and $CD3^+CD8^-IL22^+$ cells and the eosinophil counts in peripheral blood (Pearson correlation coefficient $r = 0.375$, $P = 0.016 < 0.05$; $r = 0.460$, $P = 0.002 < 0.05$). But no correlations of $CD3^{++}CD8^{++}IL17^{++}$ and $CD3^{++}CD8^{++}IL22^{++}$

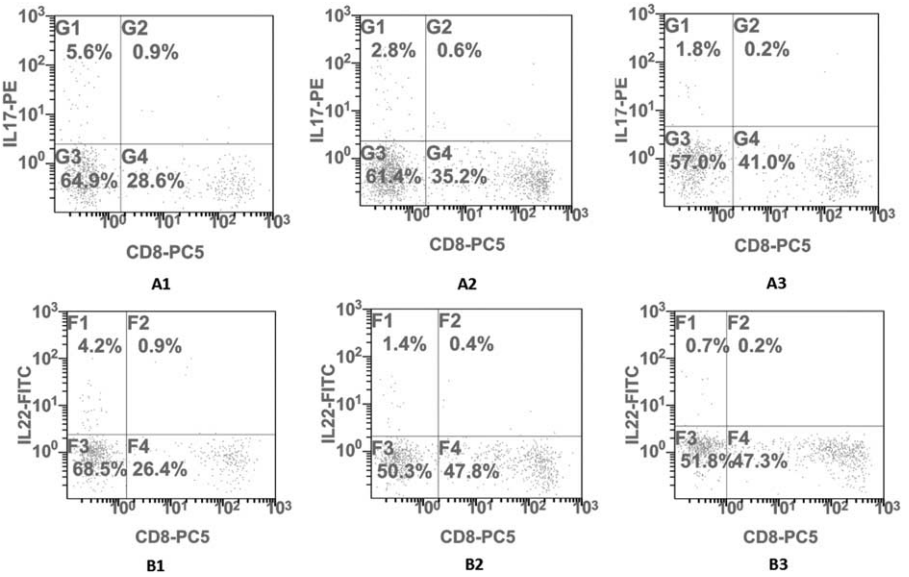

FIGURE 2. Representative profiles of circulating $CD8^-$ and $CD8^+$ IL17-/IL22-producing T cell population in formaldehyde-exposed workers and nonexposed controls. After stimulated with PMA/Ionomycin and BFA/Monensin mixture, $CD3^+CD8^+$ and $CD3^+CD8^-$ cells intracytoplasmic positive for IL17 and IL22 were assessed by flow cytometry. The upper left and right quadrants represented the percentages of $CD3^+CD8^-IL17^+/CD3^+CD8^-IL22^+$ and $CD3^+CD8^+IL17^+/CD3^+CD8^+IL22^+$ cells in the workers with ACD history (A1/B1), the workers without ACD history (A2/B2), and the controls (A3/B3), respectively.

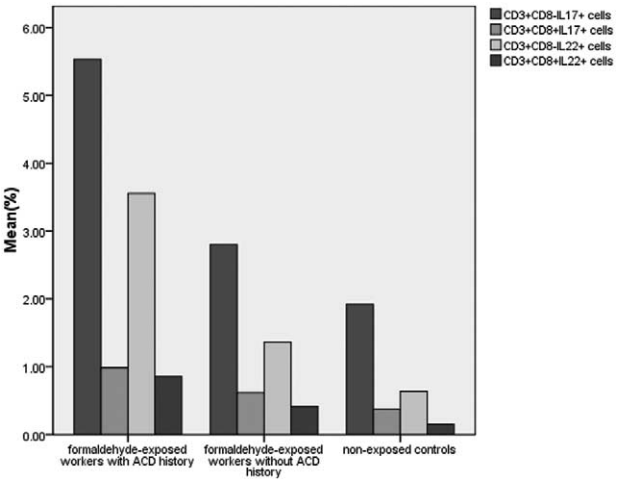

FIGURE 3. Comparisons of circulating $CD8^-$ and $CD8^+$ IL17-/IL22-producing T cell population in formaldehyde-exposed workers and nonexposed controls. The percentages of circulating $CD3^+CD8^-IL17^+$, $CD3^+CD8^-IL22^+$, and $CD3^+CD8^+IL22^+$ cells from the workers with and without ACD history were all elevated, and the elevations were more remarkable in the workers with ACD. The proportion of $CD3^+CD8^+IL17^+$ cells was also enhanced in the workers with ACD history, but not significantly different between the workers without ACD history and the controls.

proportions with the eosinophil counts were found (Pearson correlation coefficient $r = 0.075$, $P = 0.654 > 0.05$; $r = 0.147$, $P = 0.359 > 0.05$).

DISCUSSION

Th17 and Th22 cells have been implicated in the elicitation of ACD in recent studies.[11–14] But only few data were reported, concerning the associations of Th17 and Th22 cells and relevant cytokines with OACD induced by occupational hazards. It was suggested that IL17 and IL22 were involved in nickel-induced ACD,[15,18–19] and formaldehyde exposure at 0.2 ppm increased the skin IL17E mRNA expression in mice.[24] But whether formaldehyde exposure can increase Th17 and Th22 cells in the exposed workers and participate in the pathogenesis of human OACD remain to be elucidated.

Here, we observed that peripheral $CD3^+CD8^-$ cells in formaldehyde-exposed workers with and without ACD history were elevated, while $CD3^+CD8^+$ cells were declined, indicating that low-level formaldehyde exposure may increase $CD8^-$ T cells but decrease $CD8^+$ T cells. This consists with previous findings.[20,21,25] But conflicting data were also obtained in some studies.[23]

Importantly, we successfully detected circulating T lymphocytes intracellularly positive for IL17 and IL22 by flow cytometry. The $IL17^+$ and $IL22^+$ cell population were found not only in $CD3^+CD8^-$ cells but also in $CD3^+CD8^+$ cells. Moreover, the percentages of $IL17^+$ and $IL22^+$ T cells in peripheral blood of formaldehyde-exposed workers with and without ACD history were all elevated, and the elevations were more remarkable in the workers with ACD history. The data demonstrated that low-level formaldehyde exposure increased circulating IL17- and IL22-producing T cells, not only $CD4^+$ but also $CD8^+$ T cells, which might be involved in the development of OACD. Actually, other studies also suggested that not only skin-derived $CD4^+$ T cells but also $CD8^+$ T cells were able to produce IL17 and IL22.[19,26] And IL17- and IL22-producing $CD8^+$ T cells were also important for the elicitation of ACD.[27–29]

However, we did not find distinct serum concentrations of IL17 and IL22 between formaldehyde-exposed workers and the controls, although it was reported that serum level of IL22 was increased in patients with nickel contact dermatitis.[30] This suggests that formaldehyde exposure may not alter the serum levels of IL17 and IL22 before the appearance of OACD symptoms. As it was hard to obtain biopsies of normal skin from the workers and controls with no skin lesions, we were not able to further evaluate the effects of formaldehyde exposure on the expressions of Th17/Th22 cells and related cytokines in normal skin of the workers and controls.

It is known that IL17 participates in production of certain inflammatory cytokines, including granulocyte-macrophage colony-stimulating factor, tumor necrosis factor alpha, interleukin 8, C-X-C motif chemokine 10, and vascular endothelial growth factor by keratinocytes, and IL-17 and IL-22 have synergistic effects on interleukin 8 production.[31] Besides the proinflammatory function, IL22 seems to have a more protective/regenerative quality.[16] Th22 cells guarantee the skin integrity by inducing keratinocyte proliferation and migration via the signal transducer and activator of transcription 3 signal pathway.[13] These may be associated with the roles of IL17- and IL22-producing T cells for the induction of OACD.

We also observed that the percentages of $CD3^+CD8^-IL17^+$ and $CD3^+CD8^-IL22^+$ cells positively correlated to the eosinophil counts in peripheral blood, consistent with previous studies,[32] suggesting the participation of these cells in human OACD.

In summary, our data demonstrated that low-level formaldehyde exposure at proposed OEL might increase circulating Th17-/IL22-producing T cells (both $CD8^-$ and $CD8^+$), possibly involved in the development of OACD. But it may not alter the serum levels of IL17/IL22 before the appearance of OACD symptoms. Our study provides new insights into a novel mechanism for OACD, indicating that Th17/IL17 and Th22/IL22 axes may be potential targets for OACD therapy. We will follow-up with the workers next. If future studies will show that people with elevated IL17-/IL22-secreting T cells and L17/IL22 levels will develop formaldehyde-induced OACD, then this method could be used for OACD susceptibility screening during occupational health surveillance.

REFERENCES

1. Higgins CL, Palmer AM, Cahill JL, Nixon RL. Occupational skin disease among Australian healthcare workers: a retrospective analysis from an occupational dermatology clinic, 1993-2014. *Contact Dermatitis*. 2016;75:213–222.
2. Lushniak BD. The importance of occupational skin diseases in the United States. *Int Arch Occup Environ Health*. 2003;76:325–330.
3. Zuberbier T, Lötvall J, Simoens S, Subramanian SV, Church MK. Economic burden of inadequate management of allergic diseases in the European Union: a GA(2) LEN review. *Allergy*. 2014;69:1275–1279.
4. Prodi A, Rui F, Belloni Fortina A, Corradin MT, Larese Filon F. Sensitization to formaldehyde in Northeastern Italy, 1996 to 2012. *Dermatitis*. 2016;27:21–25.
5. Warshaw EM, Hagen SL, DeKoven JG, et al. Occupational contact dermatitis in North American production workers referred for patch testing: retrospective analysis of cross-sectional data from the North American Contact Dermatitis Group 1998 to 2014. *Dermatitis*. 2017;28:183–194.
6. Schwensen JF, Friis UF, Menné T, Flyvholm MA, Johansen JD. Contact allergy to preservatives in patients with occupational contact dermatitis and exposure analysis of preservatives in registered chemical products for occupational use. *Int Arch Occup Environ Health*. 2017;90:319–333.
7. DeKoven JG, Warshaw EM, Belsito DV, et al. North American contact dermatitis group patch test results 2013-2014. *Dermatitis*. 2017;28:33–46.
8. Role of the patch test in contact dermatitis. *Can Med Assoc J*. 1955;73:51.
9. Andersen KE. Systemic symptoms related to patch tests with UV curable acrylic monomers. *Contact Dermatitis*. 1986;14:180.

10. Mathias CG, Caldwell TM, Maibach HI. Contact dermatitis and gastrointestinal symptoms from hydroxyethylmethacrylate. *Br J Dermatol*. 1979; 100:447–449.
11. Hofmann MA, Kiecker F, Zuberbier T. A systematic review of the role of interleukin-17 and the interleukin-20 family in inflammatory allergic skin diseases. *Curr Opin Allergy Clin Immunol*. 2016;16:451–457.
12. Peiser M. Role of Th17 cells in skin inflammation of allergic contact dermatitis. *Clin Dev Immunol*. 2013;2013:261037.
13. Cavani A, Pennino D, Eyerich K. Th17 and Th22 in skin allergy. *Chem Immunol Allergy.* 2012;96:39–44.
14. Zhao Y, Balato A, Fishelevich R, Chapoval A, Mann DL, Gaspari AA. Th17/Tc17 infiltration and associated cytokine gene expression in elicitation phase of allergic contact dermatitis. *Br J Dermatol*. 2009;161:1301–1306.
15. Dhingra N, Shemer A, Correa da Rosa J, et al. Molecular profiling of contact dermatitis skin identifies allergen-dependent differences in immune response. *J Allergy Clin Immunol*. 2014;134:362–372.
16. Eyerich S, Eyerich K, Cavani A, Schmidt-Weber C. IL-17 and IL-22: siblings, not twins. *Trends Immunol*. 2010;31:354–361.
17. Mitra A, Raychaudhuri SK, Raychaudhuri SP. Functional role of IL-22 in psoriatic arthritis. *Arthritis Res Ther.* 2012;14:R65.
18. Larsen JM, Bonefeld CM, Poulsen SS, Geisler C, Skov L. IL-23 and T(H)17-mediated inflammation in human allergic contact dermatitis. *J Allergy Clin Immunol*. 2009;123:486–492.
19. Dyring-Andersen B, Skov L, Løvendorf MB, et al. CD4(+) T cells producing interleukin (IL)-17, IL-22 and interferon-(are major effector T cells in nickel allergy. *Contact Dermatitis*. 2013;68:339–347.
20. Sandikci M, Eren U, Kum S. Effects of formaldehyde and xylene on CD4- and CD8-positive T cells in bronchus-associated lymphoidtissue in rats. *Toxicol Ind Health*. 2007;23:471–477.
21. Fujimaki H, Kurokawa Y, Kunugita N, Kikuchi M, Sato F, Arashidani K. Differential immunogenic and neurogenic inflammatory responses in an allergic mouse model exposed to low levels of formaldehyde. *Toxicology.* 2004;197:1–13.
22. Wei H, Tan K, Sun R, Yin L, Zhang J, Pu Y. Aberrant production of Th1/Th2/Th17-related cytokines in serum of C57BL/6 mice after short-term formaldehyde exposure. *Int J Environ Res Public Health*. 2014;11: 10036–10050.
23. Hosgood 3rd HD, Zhang L, Tang X, et al. Occupational exposure to formaldehyde and alterations in lymphocyte subsets. *Am J Ind Med*. 2013;56:252–257.
24. Kim JY, Jeong MS, Park KY, Seo SJ. Aggravation of atopic dermatitis-like symptoms by consecutive low concentration of formaldehyde exposure in NC/Nga mice. *Exp Dermatol*. 2013;22:219–221.
25. Aydin S, Canpinar H, Ündeğer Ü, et al. Assessment of immunotoxicity and genotoxicity in workers exposed to low concentrations offormaldehyde. *Arch Toxicol*. 2013;87:145–153.
26. Hijnen D, Knol EF, Gent YY, et al. CD8(+) T cells in the lesional skin of atopic dermatitis and psoriasis patients are an important source of IFN-(, IL-13, IL-17, and IL-22. *J Invest Dermatol*. 2013;133:973–979.
27. He D, Wu L, Kim HK, Li H, Elmets CA, Xu H. CD8+ IL-17-producing T cells are important in effector functions for the elicitation of contact hypersensitivity responses. *J Immunol*. 2006;177:6852–6858.
28. Kish DD, Li X, Fairchild RL. CD8 T cells producing IL-17 and IFN-gamma initiate the innate immune response required for responses to antigen skin challenge. *J Immunol*. 2009;182:5949–5959.
29. Nograles KE, Zaba LC, Shemer A, et al. IL-22-producing "T22" T cells account for upregulated IL-22 in atopic dermatitis despite reduced IL-17-producing TH17 T cells. *J Allergy Clin Immunol*. 2009;123:1244–1252. e2.
30. Ricciardi L, Minciullo PL, Saitta S, Trombetta D, Saija A, Gangemi S. Increased serum levels of IL-22 in patients with nickel contact dermatitis. *Contact Dermatitis*. 2009;60:57–58.
31. Koga C, Kabashima K, Shiraishi N, Kobayashi M, Tokura Y. Possible pathogenic role of Th17 cells for atopic dermatitis. *J Invest Dermatol*. 2008;128:2625–2630.
32. Simon D, Aeberhard C, Erdemoglu Y, Simon HU. Th17 cells and tissue remodeling in atopic and contact dermatitis. *Allergy.* 2014;69:125–131.

