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Review Article

Update on the Two Contrasting Immunotoxic Effects of Formaldehyde Inhalation

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ABSTRACT

Formaldehyde (FA) is a colorless, flammable, and highly reactive one-carbon compound that is emitted from several objects at homes and workplaces. FA is also widely found in many products used in medical colleges, hospitals, and factories. Many people are exposed to FA daily via inhalation at their homes and workplaces, which contributes to environmental and occupational health problems and potentially, cancer hazards. Two types of immunomodulatory effects of FA have been widely reported. On the one hand, FA inhalation and exposure induces or exacerbates eosinophilic airway inflammation with increased bronchial hyperresponsiveness and Th2-related cytokine secretion, resulting in Th2-type immune diseases such as allergic asthma and dermatitis. On the other hand, FA exposure has no significant deleterious effect on respiratory distress and instead prevents allergic lung inflammation by suppression of T cell activity with decreased production of T cell-related cytokines. This review aimed to provide updated information on the two different immunotoxic effects induced by FA inhalation by summarizing the literature on FA exposure effects under various conditions. The insights from this review may help comprehend the mechanisms underlying the immunotoxic effects of FA and provide direction for future research.

Keywords: Immuno toxic; Formaldehyde; Pathology; Allergies; Immune responses; Inflammation

INTRODUCTION

Formaldehyde (FA) is a colorless, flammable, and highly reactive one-carbon compound present in homes and workplaces and is a common indoor air pollutant [1]. FA is widely found in many products, such as plastics, floor coverings, plywood, furniture, paints, and cosmetics [2], and is also commonly used in anatomy and pathology laboratories because of its sterilizing, preserving, and stabilizing properties [3,4]. Tang, et al. that FA concentration in indoor air is 238 μg/m^3, 256 μg/m^3, 1.37 mg/m^3, and 1.46 mg/m^3 in recently remodeled homes, offices, factories, and research laboratories and hospitals, respectively [5]. Thus, millions of people are exposed to FA daily via inhalation at their homes and workplaces [6,7], which is part of environmental and occupational health problems [8] and is a potential cancer hazard [4].

According to an FA-inhalation assessment by the US Environmental Protection Agency, FA induces adverse health effects, such as asthma, atopy, immunotoxicity, developmental toxicity, and reproductive toxicity [9]. Additionally, the International Agency for Research on Cancer has classified FA as a human carcinogen (Group 1) based on studies of nasopharyngeal cancer and leukemia [10,11]. Recent human trials and animal studies have shown that immune dysfunction induced by FA exposure may deteriorate allergic lung responses [12,13]. Moreover, immunosuppression induced by FA exposure may increase susceptibility to opportunistic infections or cancer development [14-16]. Therefore, several previous studies establish that FA exposure has toxic effects on the immune system. However, studies report inconsistent and contradictory findings on the mechanism by which the immunotoxic effects of FA are manifested-while some studies report that FA induces allergic immune responses, others report that FA has immunosuppressive effects. In this review, we summarize the updated information on the two contrasting immunotoxic effects induced by FA inhalation in the light of human trials and animal model systems.

LITERATURE REVIEW

Toxic effect of FA: Induction of allergic immune responses

FA is a well-known irritant, which may not only cause irritation but also induce acute lung injury and inflammation-related disorders, including asthma and allergies [13,17]. Several human studies have reported that exposure to FA by inhalation is associated with upper respiratory irritation [12,13,18]. Garrett, et al. showed that low-level exposure to indoor FA increased the risk of developing asthma and aggravated atopic symptoms in children [19]. Xiang, et al. [20]

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and Yue, et al. [21] revealed the dose-response relationship between indoor FA exposure and the risk of allergic asthma. Moreover, Aydin, et al. showed that the absolute number and percentage of T lymphocytes and natural killer cells significantly increase in the blood of workers occupationally exposed to FA ($p<0.05$) [18].

Jung, et al. evaluated the molecular mechanism of FA exposure-mediated airway inflammation by investigating the levels of chemokines, cytokines, and inflammatory mediators in FA-exposed mice [22]. Herein, C57BL/6 mice were exposed to 5 and 10 ppm FA 6 h/day for 5 days/week for 2 weeks. FA exposure led to airway inflammation in mice by increasing eosinophil infiltration due to the upregulation of extaxin-1, CCR3, and ICAM-1 and the altered expression of the proinflammatory cytokine (IL-1β) and Th2 cytokines (IL-4 and IL-5) through the regulation of reactive oxygen species production.

Liu, et al. Evaluated the effects of FA inhalation on lung tissue and its underlying molecular mechanisms [23]. They exposed rats to different FA concentrations (0, 0.5, 5, and 10 mg/m^3) for 8 h/day over 4 consecutive weeks. They found that exposure to 5 and 10 mg/m^3 FA induced lung injuries, such as pulmonary edema, histological changes, and inflammatory responses. Additionally, the changes in autophagy levels (including increasing ultrastructural autophagosomes and the ratio of LC3-II/LC3-I) were consistent with lung injury Deletion: [24]. Therefore, the study revealed that FA exposure triggers autophagy in alveolar epithelial cells, which might play a critical role in lung injury. Similar results were found by Wei, et al. [24], who elucidated the role of FA exposure on immunotoxicity by investigating the secretion of Th1/Th2/Th17-related cytokines in FA-exposed C57BL/6 mice (1 week or 1 month). They measured Th2 (IL-4, IL-6, and IL-10), Th1 (TNF-α, and IL-2), and Th17 (IL-17A) related cytokines using flow cytometry and found that FA exposure significantly increased the production of Th1/Th2/Th17-related cytokines in the 2.0 mg/kg FA exposure group ($p<0.05$).

Li, et al. investigated the effects of FA exposure on the development and exacerbation of allergic inflammation in two genetically different mouse strains, namely, BALB/c and C57BL/6 mice [25]. The mice were exposed to 0, 0.5, and 3.0 mg/m^3 FA for 6 h/day over 25 consecutive days, which lead to a significant increase in the secretion of Th2 (IL-4, IL-5, and IL-13)-related cytokines in a dose-dependent manner in both the strains of mice ($p<0.05$). Additionally, exposure to FA significantly induced airway inflammation (total and differential cell counts) and bronchial hyperresponsiveness ($p<0.05$). Therefore, this study showed that FA exposure can induce Th2 inflammatory responses with increased eosinophilic infiltration in both BALB/c and C57BL/6 mice.

Liu, et al. investigated the underlying role of FA exposure in combination with ovalbumin (OVA) immunization [26]. BALB/c mice were exposed to 0, 0.5, and 3.0 mg/m^3 FA for 6 h/day. This study involved 3 weeks of combined exposure and a 1-week challenge with aerosolized OVA. Exposure to 3 mg/m^3 FA alone induced mild pulmonary inflammation in the airways, while exposure to 3 mg/m^3 FA+OVA significantly increased airway hyperresponsiveness, pulmonary lung tissue damage, eosinophil infiltration, and production of proinflammatory and Th2 cytokines ($p<0.05$, $p<0.01$). This study suggests that FA exposure can induce and aggravate allergic asthma in BALB/c mice when combined with OVA immunization.

Qiao, et al. investigated FA as an irritant for the onset of asthma and as an adjuvant for the induction of allergy [27]. Herein, Wister rats were exposed to 0, 417, and 2500 ppb FA for 6 h/day. This study incorporated 3 weeks of combined exposure to OVA and FA and a 1-week challenge with aerosolized OVA. The airway reactivity, lung histological changes, pulmonary IL-4 production, and eosinophil infiltration in the OVA and FA exposure groups were significantly higher than those in the control group ($p<0.05$, $p<0.01$). This study indicated that FA may be an irritant and serve as an adjuvant for the onset of asthma or asthma-like symptoms.

Gu, et al. demonstrated that systemic allergic responses through NK-cell activation, rather than topical allergic responses, play a significant role in an experimental model exposed to gaseous FA [28]. BALB/c and C3H/He mice were sensitized by repeated i.p. injections of OVA (days 0 and 7). After a week, the mice were exposed to 0, 0.1, and 0.8 ppm FA for 24 h/day, 5 days/week for 5 weeks. This study showed that levels of OVA-specific IgE in 0.8 ppm FA exposed mice were significantly higher than those in control mice ($p<0.05$). FA exposure increases the number of splenic NK1.1+CD3-cells, which develop pulmonary eosinophilic inflammation and produce allergen-specific IgE and cytokines, as well as enhances NK-cell activity in splenic cells in both strains of mice. These results indicated that threshold concentrations (0.8 ppm defined by WHO) of FA may play a regulatory role in the systemic cell-mediated immune response.

Wu, et al. evaluated hyperresponsiveness, inflammation, and remodeling of airways using selective receptor antagonists to investigate the role of transient receptor potential (TRP) ion channels and neuropeptides in FA-induced asthma [29]. BALB/c mice were exposed to 3 mg/m^3 FA with OVA sensitization for 6 h/day, 5 days/week for 4 weeks and challenged with aerosolized OVA for a week. Treatment with the TRPA1 channel antagonist HCO30031 and the TRPV1 channel antagonist CPZ was found to reduce allergic inflammation, pulmonary tissue damage, and airway hyperresponsiveness in FA-and OVA-exposed mice. In contrast, Substance P and Calcitonin gene-related peptide were found to be involved in the development of FA-promoted asthma or asthma-like symptoms. These results suggest that FA enhances the sensitization of BALB/c mice to inhaled allergens and that it might be an underlying risk factor for an increase in asthma severity. In addition, TRPA1, TRPV1, and neuropeptides play key roles in the adjuvant effect of FA-promoted asthma or asthma-like symptoms.

Kim, et al. investigated if FA inhalation would affect the exacerbation of atopic dermatitis (AD)- Lsymptoms [30]. Herein, NC/Nga mice were exposed to 0.2 and 1.0 ppm FA inhalation. Combined exposure to 0.2 ppm FA inhalation and topical house dust mite (HDM) sensitization significantly upregulated plasma IgE and IgG2a production, Th1/Th2/Th17-related cytokines, and Cox-2 mRNA expression in the skin ($p<0.05$). These results suggest that FA exposure might be a key factor in exacerbating HDM-mediated AD-like skin inflammation.

Toxic effect of FA: Reduction of allergic immune responses

Previous animal studies and human trials have reported that FA exposure may provoke or exacerbate allergic asthma and dermatitis-like Th2 type responses [19,22-30]. However, some other studies have reported that FA exposure may not aggravate allergic responsiveness, as well as that FA exposure reduces the development of allergic lung inflammation [2,31,34-38]. Ezratty,

et al. showed that exposure to 500 μg/m^3 FA had no significant deleterious effect on airway allergen responsiveness in patients with intermittent asthma and that FA exposure instead showed a protective effect on asthmatic responses [2]. Hosgood, et al. reported that FA-exposed workers showed reduced counts of the major lymphocyte subset, including NK cells, B cells, and T cells [31]. These results could potentially lead to alterations in immune function and antitumor responses that also manifest as cancer development and progression. Zhong, et al. showed that FA exposure disrupts hematopoietic function and produces leukemia-related chromosomal changes in FA-exposed workers, raising concerns about the leukemogenic potential of occupational and environmental FA exposure [32]. Similar results were obtained by Hauptmann, et al., who showed that the duration of embalming practice and related FA exposure in the funeral industry was associated with a significant risk of mortality from myeloid leukemia (p=0.024) [33].

Park, et al. investigated the effects of FA exposure on immune responses by evaluating T cell population and cytokine expression in the spleen of an FA-exposed mouse model [34]. BALB/c mice were exposed to 0, 1.38, and 5.36 mg/m^3 FA 4 h/day for 5 days/week for 2 weeks. FA exposure suppressed effector T cell activity by decreasing T cell-related cytokine secretion and mRNA expression. FA exposure also induced the differentiation of Treg cells via calcineurin-NFAT signaling activation, which may play a critical role in the progression of Foxp3-induced immunosuppression. These results suggest that FA exposure leads to the development of an immunosuppressive environment, which leads to increased susceptibility to opportunistic infections, and cancer development and progression.

Ohtsuka, et al. reported that FA exposure-induced changes in Th1/Th2 related cytokine expressions in the nasal mucosa [35]. Brown Norway and Fisher 344 rats were exposed to 1% FA aerosol 3 h/day for 5 consecutive days. FA exposure led to mucosal lesions characterized by degeneration and/or desquamation of epithelial cells with neutrophilic infiltration, as well as significantly decreased levels of Th1-related cytokines (IFN-γ and IL-2) ($p<0.05$). The Th2-related cytokines IL-4 and IL-5 also tended to be depressed. Similar results were found by Wei, et al., who elucidated the role of FA exposure on immunotoxicity by investigating the secretion of Th1/Th2/Th17-related cytokines in FA-exposed C57BL/6 mice (1 week or 1 month). FA exposure led to slightly lower levels of Th1/Th2/Th17-related cytokines in the 0.5 mg/kg FA exposed group.

Fujimaki, et al. Reported the effects of FA exposure on immunogenic and neurogenic inflammatory responses in a mouse model of asthma [17]. C3H/He mice were immunized with OVA and then exposed to 0, 80, 400, and 2000 ppb FA for 16 h/day, 5 days/week for 12 weeks. The production of IL-1β in bronchoalveolar lavage fluid significantly decreased in FA-exposed mice than in 0 ppb FA-exposed control mice ($p<0.05$). Exposure to 400 ppb FA resulted in a marked decline in the production of OVA-specific IgG1 and IgG3 in mice ($p<0.05$). In addition, the levels of nerve growth factor significantly decreased in 80 and 400 ppb FA-exposed mice compared to control mice ($p<0.01$).

Li, et al. Reported the effect of FA exposure on the development and exacerbation of allergic inflammation in two genetically different mouse strains, BALB/c and C57BL/6 [25]. The mice were exposed to 0, 0.5, and 3.0 mg/m^3 FA with OVA sensitization for 6 h/day over 25 consecutive days and challenged with aerosolized OVA during the last week. Combined FA exposure and OVA immunization resulted in markedly decreased Th2 cytokine levels (IL-4, IL-5, and IL-13) and eosinophil infiltration in the bronchoalveolar lavage fluid ($p<0.05$). Additionally, bronchial hyperresponsiveness in sensitized mice exposed to 3.0 mg/m^3 FA was significantly lower than that in sensitized mice not exposed to FA ($p<0.05$).

Maiellor, et al. reported the effects of low-dose FA exposure on pregnant rats and its effects on the development of allergic lung inflammation in offspring [36]. Pregnant Wistar rats were exposed to 0.75 ppm FA for 1 h/day, 5 days/week for 21 days. After 30 days of age, the offspring were sensitized with OVA and challenged with aerosolized OVA to develop allergic lung inflammation and tracheal hyperresponsiveness. Low-dose FA exposure in pregnancy suppressed the development of allergic lung inflammation and tracheal hyperresponsiveness in offspring by mechanics mediated by reduced anaphylactic antibody synthesis and IL-6 and TNF-α secretion. Oxidative stress in the uterine environment was evident at the time of delivery, as quantified by elevated Cox-1 expression and reduced cNOS and SOD-2 in the uterus.

Kim, et al. investigated the cytotoxic effects of FA on NK cells and tumorigenicity [37]. C57BL/6 mice were exposed to 5 and 10 ppm FA for 6 h/day, 5 days/week for 2 weeks. Before FA exposure, the tumor-bearing FA exposure group was injected subcutaneously with 5 × 10^4 B16F10 melanoma cells. The exposure to FA reduced not only the number of NK cells but also the expression of NK cell-specific receptors. Exposure to FA also decreased NK cytolytic activity and the expression of IFN-γ, perforin, and CD122, whose expression is dependent on NK cell development. Furthermore, the mass of the tumor and the concentration of extravascular polymorphonuclear leukocytes in FA-exposed tumor-bearing mice were greater than those in unexposed tumor-bearing control mice, suggesting that FA exposure exacerbates tumor progression. Moreover, the number and cytolytic activity of NK cells was also reduced in B16F10 tumor-bearing mice exposed to FA. These findings indicate that FA exposure may induce tumor progression by impairing NK cell function and differentiation.

CONCLUSION

In this review, we summarized the basic mechanisms and literature on the two different immunotoxic effects induced by FA inhalation. Some studies have reported that FA exposure provokes or exacerbates eosinophilic airway inflammation with increased bronchial hyperresponsiveness and Th2-related cytokine secretion, resulting in Th2-type immune diseases such as allergic asthma and dermatitis, whereas other studies have found that FA exposure has no significant deleterious effect on respiratory distress and that FA exposure prevents allergic lung inflammation by suppressing T cell activity and decreasing the production of T cell-related cytokines. Little is known about these contrasting toxic effects and the molecular mechanisms of FA exposure. Such disparate immune responses following FA exposure likely exist due to differences in species and strains of animal models, FA concentrations and duration of FA exposure, and experimental protocols. Therefore, further studies under various conditions are essential to investigate the impact of FA exposure on the immune system. We hope that this review may provide insights for systematic future investigations on the FA effects.

REFERENCES

1. Kilburn KH. Indoor air effects after building renovation and in manufactured homes. Am J Med Sci. 2000;320:249-254.
2. Ezratty V, Bonay M, Neukirch C, Orset-Guillossou G, Dehoux M. Effect of formaldehyde on asthmatic response to inhaled allergen challenge. Environ Health Perspect. 2007;115:210-214.
3. Bernardini L, Barbosa E, Charão MF, Brucker N. Formaldehyde toxicity reports from in vitro and *in vivo* studies: A review and updated data. Drug Chem Toxicol. 2020;1-13.
4. Costa S Pina C, Coelho P, Costa C, Silva S, Porto B. Occupational exposure to formaldehyde: genotoxic risk evaluation by comet assay and micronucleus test using human peripheral lymphocytes. J Toxicol Environ Health Part A. 2011;74:1040-1051.
5. Tang X, Bai Y, Duong A, Smith MT, Li L. Formaldehyde in China: Production, consumption, exposure levels, and health effects. Environ Int. 2009;35:1210-1224.
6. Santos-Franco DLA, Domingos HV, Damazo AS, Breithaupt-Faloppa AC, De Oliveira APL, Costa SKP, et al. Reduced allergic lung inflammation in rats following formaldehyde exposure: Long-term effects on multiple effector systems. Toxicology. 2009;256:157-163.
7. Songur A, Akpolat N, Kus I, Ozen OA, Zararsiz I. The effects of the inhaled formaldehyde during the early postnatal period in the hippocampus of rats: a morphological and immunohistochemical study. Neurosci Res Commun. 2003;33:168-178.
8. Franco LDSA. Domingos HV, De Oliveira APL, Breithaupt-Faloppa AC, Peron JPS. Differential effects of formaldehyde exposure on the cell influx and vascular permeability in a rat model of allergic lung inflammation. Toxicol Lett. 2010;197:211-218.
9. US EPA (United States Environmental Protection Agency). Toxicological review of Formaldehyde-Inhalation assessment. 2010.
10. Baan R, Grosse Y, Straif K, Secretan B, El Ghissassi F. A review of human carcinogens-part F: Chemical agents and related occupations. Lancet Oncol. 2009;10:1143-1144.
11. Kleinnijenhuis AJ, Staal YC, Duistermaat E, Engel R, Woutersen RA. The determination of exogenous formaldehyde in blood of rats during and after inhalation exposure. Food Chem Toxicol. 2013;52:105-112.
12. Salonen H, Pasanen AL, Lappalainen S, Riuttala H, Tuomi T. Volatile organic compounds and formaldehyde as explaining factors for sensory irritation in office environments. J Occup Environ Hyg. 2009;6:239-247.
13. Kim KH, Jahan SA, Lee JT. Exposure to formaldehyde and its potential human health hazards. J Environ Sci Health C Environ Carcinog Ecotoxicol Rev. 2011;29:277-299.
14. Mc Gregor D, Bolt H, Cogliano V, Richter-Reichhelm HB. Formaldehyde and glutaraldehyde and nasal cytotoxicity: case study within the context of the 2006 IPCS Human Framework for the Analysis of a cancer mode of action for humans. Crit Rev Toxicol. 2006;36:821-835.
15. Sul D, Kim H, Oh E, Phark S, Cho E. Gene expression profiling in lung tissues from rats exposed to formaldehyde. Arch Toxicol. 2007;81:589-597.
16. Thompson CM, Grafström RC. Considerations for the implausibility of leukemia induction by formaldehyde. Toxicol Sci. 2011;120:230-232.
17. Fujimaki H, Kurokawa Y, Kunugita N, Kikuchi M, Sato F. Differential immunogenic and neurogenic inflammatory responses in an allergic mouse model exposed to low levels of formaldehyde. Toxicology. 2004;197: 1-13.
18. Aydin S, Canpınar H, Undeger U, Guç D, Çolakoglu M. Assessment of immunotoxicity and genotoxicity in workers exposed to low concentrations of formaldehyde. Arch Toxicol. 2013;87:145-153.
19. Garrett MH, Hooper MA, Hooper BM, Rayment PR, Abramson MJ. Increased risk of allergy in children due to formaldehyde exposure in homes. Allergy. 1999;54:330-337.
20. Xiang J. Analysis on 60 cases of allergic bronchial asthma caused by gaseous formaldehyde. J Wenzhou Med Coll. 1996;26:47-48.
21. Yue W, Jin XB, Pan XC, Ding J. Relationship between indoor air formaldehyde exposure and allergic asthma in adults. Chin J Public Health. 2004;20:904-906.
22. Jung WW, Kim EM, Lee EH, Yun HJ, Ju HR. Formaldehyde exposure induces airway inflammation by increasing eosinophil infiltrations through the regulation of reactive oxygen species production. Environ Toxicol Pharmacol. 2007;24:174-182.
23. Liu Q, Zhou DX, Lv MQ, Ge P, Li YX. Formaldehyde inhalation triggers autophagy in rat lung tissues. Toxicol Ind Health. 2018;34:834-841.
24. Wei H, Tan K, Sun R, Yin L, Zhang J. 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.
25. Li L, Hua L, He Y, Bao Y. Differential effects of formaldehyde exposure on airway inflammation and bronchial hyperresponsiveness in BALB/c and C57BL/6 mice. PLoS One. 2017;12:0179231.
26. Liu D, Zheng Y, Li B, Yao H, Li R. Adjuvant effects of gaseous formaldehyde on the hyper-responsiveness and inflammation in a mouse asthma model immunized by ovalbumin. J Immunotoxicol. 2011;8:305-314.
27. Qiao Y, Li B, Yang G, Yao H, Yang J. Irritant and adjuvant effects of gaseous formaldehyde on the ovalbumin-induced hyperresponsiveness and inflammation in a rat model. Inhal Toxicol. 2009;21:1200-1207.
28. Gu YH, Fujimiya Y, Kunugita N. Long-term exposure to gaseous formaldehyde promotes allergen-specific IgE-mediated immune responses in a murine model. Hum Exp Toxicol. 2008;27:37-43.
29. Wu Y, You H, Ma P, Li L, Yuan Y. Role of transient receptor potential ion channels and evoked levels of neuropeptides in a formaldehyde-induced model of asthma in BALB/c mice. PLoS One. 2013;8: 62827.
30. 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.
31. Hosgood III HD, Zhang L, Tang X, Vermeulen R, Hao Z. Occupational exposure to formaldehyde and alterations in lymphocyte subsets. A J Ind Med. 2013;56:252-257.
32. Zhang L, Tang X, Rothman N, Vermeulen R, Ji Z. Occupational exposure to formaldehyde, hematotoxicity, and leukemia-specific chromosome changes in cultured myeloid progenitor cells. Cancer Epidemiol Biomark Prev. 2010;19:80-88.
33. Hauptmann M, Stewart PA, Lubin JH, Beane Freeman LE, Hornung RW. Mortality from lymphohematopoietic malignancies and brain cancer among embalmers exposed to formaldehyde. J Natl Cancer Inst. 2009;101:1696-1708.
34. Park J, Yang HS, Song MK, Kim DI, Lee K. Formaldehyde exposure induces regulatory T cell-mediated immunosuppression *via* calcineurin-NFAT signalling pathway. Sci Rep. 2020;10:1-10.
35. Ohtsuka R, Shutoh Y, Fujie H, Yamaguchi S, Takeda M. Rat strain difference in histology and expression of Th1-and Th2-related cytokines in nasal mucosa after short-term formaldehyde inhalation. Exp Toxicol Pathol. 2003;54:287-291.
36. Maiellaro M, Correa-Costa M, Vitoretti LB, Júnior JAG, Câmara NOS. Exposure to low doses of formaldehyde during pregnancy suppresses the development of allergic lung inflammation in offspring. Toxicol Appl Pharmacol. 2014;278:266-274.
37. Kim EM, Lee HY, Lee EH, Lee KM, Park M. Formaldehyde exposure impairs the function and differentiation of NK cells. Toxicol Lett. 2013;223:154-161.