Available online at www.sciencedirect.com

ScienceDirect

www.elsevier.com/locate/jes

JES JOURNAL OF ENVIRONMENTAL SCIENCES

www.jesc.ac.cn

Study of the effects of bisphenol A using human fetal lung fibroblasts

*Jeffrey Tao, Lily Xiao Jing Sun, X. Chris Le**

Division of Analytical and Environmental Toxicology, Department of Laboratory Medicine and Pathology, University of Alberta, Edmonton, Alberta, T6G 2G3, Canada

ARTICLE INFO

Available online 20 September 2016

Keywords:
Bisphenol A (BPA)
Estrogen receptors
Endocrine disruptors
Developmental effects
Immune effects
Cytokines
Asthma

Bisphenol A (BPA, 2,2-bis(4-hydroxyphenyl) propane; CAS# 80-05-7) is a highly produced industrial chemical, with an estimated four billion kilograms produced worldwide each year (reviewed in Vandenberg et al., 2010). BPA serves as a monomer in the manufacture of polycarbonate, a hard, clear plastic. Polycarbonate plastics are used in many consumer products, such as reusable water bottles. BPA is also widely used to make epoxy resins, which are used as coating on the inside of some metal-based food and beverage cans to protect the food from direct contact with metal surfaces. BPA has been used in food packaging since the 1960s. Small amounts of BPA can be leached out from the containers into food and drinks. Because of the prevalence of BPA in food and beverage containers, humans are exposed to measurable levels of BPA (Krishnan et al., 1993; Staples et al., 1998; Kang et al., 2006; Calafat et al., 2008; Vandenberg et al., 2010; Wang et al., 2014). For example, the general population in the United States consumes a median BPA amount of 34 nanograms per kilogram body weight per day (34 ng/kg day) (Lakind and Naiman, 2011). The major route of human exposure to BPA is through ingestion, although dermal exposure to BPA is also possible (Liao and Kannan, 2011), because newspapers, flyers, tickets, receipts (thermal paper), and magazines also contain BPA.

Many studies have focused on the effects of BPA, including its possible links to diabetes, obesity, reproductive disorders, cardiovascular diseases, birth defects, kidney diseases, and cancer (Wetherill et al., 2007; Rezg et al., 2014; Li et al., 2015; Yin et al., 2015; Seachrist et al., 2016). BPA is known for its endocrine-disrupting estrogenic effects, which have been referenced to contribute to chronic diseases (Wetherill et al., 2007; Rubin, 2011; Rezg et al., 2014). Canada, the European Union, the United States, and several countries in Asia have banned the use of BPA for the production of baby bottles (EUR-Lex, 2011; Government of Canada, 2013; USFDA, 2014; Baluka and Rumbeiha, 2016). However, conflicting findings on BPA toxicity and the reported differences between low-dose and high-dose effects have led to continuing debate over the effects of BPA and its mechanism(s) of action (Vandenberg et al., 2009; Valentino et al., 2016). As a result, several legislations have deemed BPA irrelevant to human health and still permit the wide use of BPA for the production of select materials.

An active topic of research focuses on the role of BPA in the development of asthma (Robinson and Miller, 2015). Most experiments on this topic have been performed on mice pups, and these experiments demonstrated the adverse effects of BPA on normal fetal lung and airway development. Fetal lung impairments resulted from high concentrations of BPA in maternal diet. Effects included diminished alveolar airspace, increased alveolar septa thickness and immature alveolar epithelial cells (Hijazi et al., 2015). In addition, exposure to high concentrations of BPA *in utero* alters prenatal development of the murine immune system, leading to allergic sensitization and eosinophil recruitment that result in asthma phenotypes after birth (Nakajima et al., 2012; Midoro-Horiuti et al., 2010). However, other studies suggest that exposure to BPA during fetal stages of lung development does not cause any significant allergic lung inflammation observable in adulthood (Bauer

* *Corresponding author*. E-mail: xc.le@ualberta.ca (X. Chris Le).

http://dx.doi.org/10.1016/j.jes.2016.09.001

et al., 2012). Even with studies that demonstrate clear linkage between BPA and asthma, it is difficult to reliably translate the results from high-dose exposure in animal models to low-dose scenarios in human populations.

Epidemiological studies of human populations suggest that BPA contributes to the prenatal and postnatal development of asthma. On average, the concentration of BPA in the placenta during pregnancy ranges from 1.0 to 104.9 ng/g and the average fetal plasma concentrations ranges from 0.2 to 9.2 ng/mL (Schonfelder et al., 2002). Prenatal exposure to BPA has been correlated with diminished lung function in young children less than 5 years old (Spanier et al., 2014). Urinary BPA concentrations in early childhood were also correlated with asthma development later in childhood in a cohort study (Donohue et al., 2013). However, the same study suggests that prenatal BPA exposure did not correlate with the prevalence of asthma in the children. Thus, there appears to be conflicting results between pre/postnatal BPA exposure and childhood development of asthma, which could be due to the variations in the populations studied.

Attempting to gain further insights into the potential role of BPA in possible asthma development, Mahemuti et al. (2016) tested the effects of BPA on developmental and immune responses in human fetal lung fibroblasts (hFLFs) (Fig. 1). Performing such an *in vitro* experiment complements animal and epidemiological studies by elucidating direct cellular responses of human lung cell-lines to BPA that may underlie asthma phenotypes. Studying fibroblasts separated from *in vivo* conditions is appealing because these fibroblasts respond to and also produce inflammatory mediators (Alkhouri et al., 2014), and they secrete extracellular matrix for tissue remodeling that may become aberrant in lung diseases, including asthma (Fixman et al., 2007; Dijkstra et al., 2006). Previously, *in vitro* experiments have been beneficial when illustrating causality between BPA and chronic diseases. For example, epidemiological findings that correlate BPA and type-2 diabetes have been further supported by *in vitro* findings that show that physiologically relevant concentrations of BPA can alter immune factor expression and insulin signaling in 3 T3-L1 pre-adipocytes (Ahmadkhaniha et al., 2014; Valentino et al., 2013). Studying the effects of BPA on hFLFs may help confirm the presence or absence of asthmogenic cellular pathways underlying the correlations between BPA and asthma identified in epidemiological and animal studies.

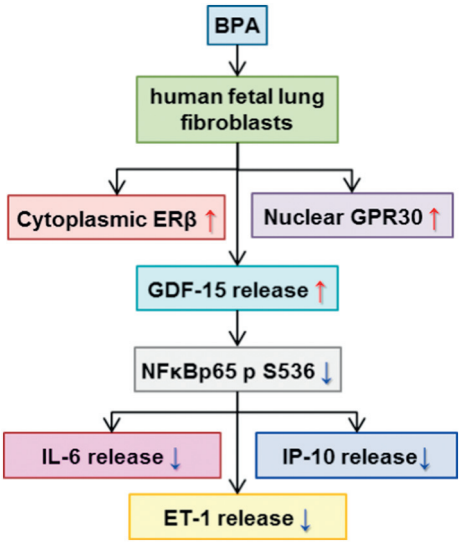

Fig. 1 – Effects of BPA in human fetal lung fibroblasts, showing increased release of growth differentiation factor-15 (GDF-15) and decreased phosphorylation of nuclear factor kappa B (NFκB) p65 at serine 536, leading to decreased release of NFkB-regulated immune and developmental modulators, interleukin 6(IL-6), interferon gamma-induced protein 10 (IP-10), and endothelin 1 (ET-1). These changes paralleled with increased expression of cytoplasmic estrogen receptor β (ERβ) and nuclear G-protein coupled estrogen receptor 30 (GPR30). (Adapted from Mahemuti et al., 2016).

Because BPA is an estrogen analog capable of interrupting signaling pathways of estrogen receptors (ERs), it is plausible that BPA may have similar effects to those of estrogens. Estrogen receptor alpha (ERα) and beta (ERβ) are expressed in the lung in response to exposure to estrogens (Mollerup et al., 2002; Ciana et al., 2001; Marino et al., 2006). Estrogens also affect pulmonary alveolar development (Massaro and Massaro, 2004; Massaro et al., 2007). Lung pathology often has signs of altered ER expression (Logginidou et al., 2000). In addition, BPA may also act through the membrane receptor G protein-coupled receptor 30 (GPR30) (Prossnitz et al., 2007) and affect downstream messengers in the lung, which has been implicated in other lung pathologies (Zhang et al., 2014). As a result, Mahemuti et al. (2016) sought to detect the presence of estrogen receptors ERα, ERβ, and GPR30 in hFLFs. Using fluorescence microscopy, they found that all three ERs were stained in the nuclei and cytoplasm, with a denser localization within the nuclei. The presence of ERs in the nuclei and cytoplasm of hFLFs suggests the potential for BPA to disrupt airway development and function through ER signaling (Bonds and Midoro-Horiuti, 2013).

Maternal and fetal BPA concentrations in the serum and placenta are well-documented (Schonfelder et al., 2002), but the amount of BPA absorbed into lung cells, specifically hFLFs, was not known. Mahemuti et al. (2016) used gas chromatography separation with mass spectrometry detection to measure the intracellular concentration of BPA. They detected the highest intracellular BPA levels to be 23 μmol/L in hFLFs incubated with 100 μmol/L BPA. However, they found that the ratio of intracellular to extracellular BPA concentrations decreased with increasing BPA administration. They suggest that either the BPA binding sites in hFLFs could have been saturated or that BPA excretion could have equilibrated with BPA absorption at the higher levels of exposure to BPA.

BPA appears to cause mitochondria-mediated apoptosis and necrosis in other tissue cells (Xia et al., 2014; Lin et al., 2013; Neri et al., 2015), but it is unknown if BPA induces similar effects in lung cells. Mahemuti et al. (2016) show that hFLFs seemed to survive even 100 μmol/L BPA in the culture medium. However, the hFLFs had a fibrotic appearance, which is indicative of cell stress and injury (Cheresh et al., 2013). Therefore, it is likely that high doses of BPA stressed the hFLFs enough to activate an adaptive response. This coincides with their finding of increased growth differentiation factor 15 (GDF15), which could be responsible for the fibrotic appearance (Lambrecht et al., 2014), and stress resistance (Nickel et al., 2011;

Zimmers et al., 2005; Schober et al., 2001). Furthermore, they also found lowered extracellular protease activity, which may help alleviate excessive oxidative stress in lung fibroblasts (Aoshiba et al., 2001).

The proposed adaptive response may explain the observed anti-inflammatory response after incubation with 100 μmol/L BPA (Mahemuti et al., 2016). The increased GDF15, a cytokine released from macrophages, may have initiated a protective anti-inflammatory response in hFLFs that has been observed in other diseases (Breit et al., 2011). Interferon gamma-induced protein 10 (IP-10), a pro-inflammatory factor and airway allergen (Medoff et al., 2002), was significantly lowered by 100 μmol/L BPA. Furthermore, phosphorylation of nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) subunit p56 at the S536 residue, which is a transcription modulator for inflammatory factors (Hochrainer et al., 2013; Li and Verma, 2002; Tak and Firestein, 2001), was found to be decreased. However, the finding of anti-inflammation (Mahemuti et al., 2016) appears to conflict with the conventional pathogenesis of asthma that involves the recruitment of inflammatory cells, such as eosinophils, mast cells, and neutrophils (NAEPP, 2007), which are linked with increased NF-κB, IP-10 and IL-6 (Medoff et al., 2002; Sheller et al., 2009; Rincon and Irvin, 2012). However, IL-6 might not be indicative of inflammation in the lung, as DiCosmo et al. (1994) found that IL-6 mediated airway resistance could be independent of inflammation. Instead, the finding by Mahemuti et al. (2016) of decreased IL-6 may indicate potential interruptions to airway development, in which IL-6 has been found to promote the maturation of fetal lungs and protect against the development of respiratory diseases (Shimoya et al., 2000). Indeed, BPA impairment of fetal lung development is further supported through their finding of decreased endothelin-1 (ET-1), which is known for its mitogenic and functional role in developing airways (Goldie et al., 1995). Additionally, they tested whether decreased release of ET-1 was due to BPA-activated ER signaling by applying estrogen and BPA antagonists MPP, PHTPP, and G15. They found that the antagonists did not reverse the BPA-induced decreases in ET-1 release. This could indicate the involvement of other processes.

The observed responses of hFLF to BPA in the Mahemuti et al. (2016) study laid the groundwork for future *in vitro* studies to determine potential mechanisms underlying the contribution of BPA to asthma development. The study shows that BPA may affect ER signaling and stress-resistance/inflammatory pathways in hFLFs, although the doses of BPA that evoked an observable response were 3–5 magnitudes higher than the 0.87–87 nmol/L (0.2–20 ng/mL) of BPA found in maternal and fetal bodily fluids (Vandenberg et al., 2007).

Several future directions could be considered utilizing fetal lung cells for *in vitro* studies of BPA. For example, the chosen short-term, 24-hr exposure of BPA may only stimulate acute stress-resistant and anti-inflammatory responses in the hFLFs. More investigation into the responses to the chronic exposure of hFLFs to BPA for longer exposure times of days to weeks may help elucidate low-dose effects of BPA; after all, fetuses would be exposed to months of BPA during pregnancy. Concurrently, monitoring additional factors that directly promote fibrosis and inflammation, such as macrophage recruitment, matrix metalloproteinases (Royce et al., 2012; Linthout et al., 2011), interleukins, and lymphocytes (Amin et al., 2000), may provide useful insights. These factors could play a role in fetal airway structural changes and asthma development before birth. The presence of apoptotic and necrotic factors, such as caspases and cytosolic adenylate kinase, could be evaluated to understand the cytotoxicity of BPA. Lastly, applying the *in vitro* approach of studying direct cellular responses to BPA to already differentiated lung cells, such as endothelial, smooth muscle, and alveolar cells, would help illustrate impairments to fetal lung tissue by BPA.

Acknowledgments

We thank Alberta Health, Alberta Innovates, the Canada Research Chairs Program, the Canadian Institutes of Health Research, and the Natural Sciences and Engineering Research Council of Canada for their support.

REFERENCES

Ahmadkhaniha, R., Mansouri, M., Yunesian, M., Omidfar, K., Jeddi, M.Z., Larijani, B., et al., 2014. Association of urinary bisphenol A concentration with type-2 diabetes mellitus. J. Environ. Health Sci. Eng. 12 (1), 64. http://dx.doi.org/10.1186/2052-336X-12-64.

Alkhouri, H., Poppinga, W.J., Tania, N.P., Ammit, A., Schuliga, M., 2014. Regulation of pulmonary inflammation by mesenchymal cells. Pulm. Pharmacol. Ther. 29 (2), 156–165. http://dx.doi.org/10.1016/j.pupt.2014.03.001.

Amin, K., Ludviksdottir, D., Janson, C., Nettelbladt, O., Bjornsson, E., Roomans, G.M., et al., 2000. Inflammation and structural changes in the airways of patients with atopic and nonatopic asthma. BHR group. Am. J. Respir. Crit. Care Med. 162 (6), 2295–2301. http://dx.doi.org/10.1164/ajrccm.162.6.9912001.

Aoshiba, K., Yasuda, K., Yasui, S., Tamaoki, J., Nagai, A., 2001. Serine proteases increase oxidative stress in lung cells. Am. J. Physiol. Lung Cell Mol. Physiol. 281 (3), L556–L564.

Baluka, S.A., Rumbeiha, W.K., 2016. Bisphenol A and food safety: lessons from developed to developing countries. Food Chem. Toxicol. 92, 58–63. http://dx.doi.org/10.1016/j.fct.2016.03.025.

Bauer, S.M., Roy, A., Emo, J., Chapman, T.J., Georas, S.N., Lawrence, B.P., 2012. The effects of maternal exposure to bisphenol A on allergic lung inflammation into adulthood. Toxicol. Sci. 130 (1), 82–93. http://dx.doi.org/10.1093/toxsci/kfs227.

Bonds, R.S., Midoro-Horiuti, T., 2013. Estrogen effects in allergy and asthma. Curr. Opin. Allergy Clin. Immunol. 13 (1), 92–99. http://dx.doi.org/10.1097/ACI.0b013e32835a6dd6.

Breit, S.N., Johnen, H., Cook, A.D., Tsai, V.W., Mohammad, M.G., Kuffner, T., et al., 2011. The TGF-beta superfamily cytokine, MIC-1/GDF15: a pleotrophic cytokine with roles in inflammation, cancer and metabolism. Growth Factors 29 (5), 187–195. http://dx.doi.org/10.3109/08977194.2011.607137.

Calafat, A.M., Ye, X.Y., Wong, L.Y., Reidy, J.A., Needham, L.L., 2008. Exposure of the US population to bisphenol A and 4-tertiary-octylphenol: 2003–2004. Environ. Health Perspect. 116 (1), 39–44. http://dx.doi.org/10.1289/ehp.10753.

Cheresh, P., Kim, S.J., Tulasiram, S., Kamp, D.W., 2013. Oxidative stress and pulmonary fibrosis. Biochim. Biophys. Acta 1832 (7), 1028–1040. http://dx.doi.org/10.1016/j.bbadis.2012.11.021.

Ciana, P., Di Luccio, G., Belcredito, S., Pollio, G., Vegeto, E., Tatangelo, L., et al., 2001. Engineering of a mouse for the in vivo profiling of estrogen receptor activity. Mol. Endocrinol. 15 (7), 1104–1113. http://dx.doi.org/10.1210/mend.15.7.0658.

DiCosmo, B.F., Geba, G.P., Picarella, D., Elias, J.A., Rankin, J.A., Stripp, B.R., et al., 1994. Airway epithelial cell expression of

interleukin-6 in transgenic mice. Uncoupling of airway inflammation and bronchial hyperreactivity. J. Clin. Invest. 94 (5), 2028–2035. http://dx.doi.org/10.1172/JCI117556.

Dijkstra, A., Howard, T.D., Vonk, J.M., Ampleford, E.J., Lange, L.A., Bleecker, E.R., et al., 2006. Estrogen receptor 1 polymorphisms are associated with airway hyperresponsiveness and lung function decline, particularly in female subjects with asthma. J. Allergy Clin. Immunol. 117 (3), 604–611. http://dx.doi.org/10.1016/j.jaci.2005.11.023.

Donohue, K.M., Miller, R.L., Perzanowski, M.S., Just, A.C., Hoepner, L.A., Arunajadai, S., et al., 2013. Prenatal and postnatal bisphenol A exposure and asthma development among inner-city children. J. Allergy Clin. Immunol. 131 (3), 736–742. http://dx.doi.org/10.1016/j.jaci.2012.12.1573.

EUR-Lex, 2011. Commission implementing regulation (EU) no 321/2011 of 1 April 2011 amending regulation (EU) no 10/2011 as regards the restriction of use of bisphenol A in plastic infant feeding bottles. Available at: http://eur-lex.europa.eu/legal-content/EN/ALL/?uri=CELEX%3A32011R0321 (Accessed on August 30, 2016).

Fixman, E.D., Stewart, A., Martin, J.G., 2007. Basic mechanisms of development of airway structural changes in asthma. Eur. Respir. J. 29 (2), 379–389. http://dx.doi.org/10.1183/09031936.00053506.

Goldie, R.G., Henry, P.J., Knott, P.G., Self, G.J., Luttmann, M.A., Hay, D.W., 1995. Endothelin-1 receptor density, distribution, and function in human isolated asthmatic airways. Am. J. Respir. Crit. Care Med. 152 (5 Pt 1), 1653–1658. http://dx.doi.org/10.1164/ajrccm.152.5.7582310.

Government of Canada, 2013. Bisphenol A (BPA). Available at: http://healthycanadians.gc.ca/healthy-living-vie-saine/environment-environnement/home-maison/bisphenol_a-eng.php (Accessed on August 30, 2016).

Hijazi, A., Guan, H., Cernea, M., Yang, K., 2015. Prenatal exposure to bisphenol A disrupts mouse fetal lung development. FASEB J. 29 (12), 4968–4977. http://dx.doi.org/10.1096/fj.15-270942.

Hochrainer, K., Racchumi, G., Anrather, J., 2013. Site-specific phosphorylation of the p65 protein subunit mediates selective gene expression by differential NF-kappaB and RNA polymerase II promoter recruitment. J. Biol. Chem. 288 (1), 285–293. http://dx.doi.org/10.1074/jbc.M112.385625.

Kang, J.H., Kondo, F., Katayama, Y., 2006. Human exposure to bisphenol A. Toxicology 226 (2/3), 79–89. http://dx.doi.org/10.1016/j.tox.2006.06.009.

Krishnan, A.V., Stathis, P., Permuth, S.F., Tokes, L., Feldman, D., 1993. Bisphenol-A: an estrogenic substance is released from polycarbonate flasks during autoclaving. Endocrinology 132 (6), 2279–2286. http://dx.doi.org/10.1210/endo.132.6.8504731.

Lakind, J.S., Naiman, D.Q., 2011. Daily intake of bisphenol A and potential sources of exposure: 2005–2006 National Health and Nutrition Examination Survey. J. Expo. Sci. Environ. Epidemiol. 21 (3), 272–279. http://dx.doi.org/10.1038/jes.2010.9.

Lambrecht, S., Smith, V., De Wilde, K., Coudenys, J., Decuman, S., Deforce, D., et al., 2014. Growth differentiation factor 15, a marker of lung involvement in systemic sclerosis, is involved in fibrosis development but is not indispensable for fibrosis development. Arthritis Rheum. 66 (2), 418–427. http://dx.doi.org/10.1002/art.38241.

Li, Q., Verma, I.M., 2002. NF-kappaB regulation in the immune system. Nat. Rev. Immunol. 2 (10), 725–734. http://dx.doi.org/10.1038/nri910.

Li, J., Fu, K.Z., Vemula, S., Le, X.C., Li, X.-F., 2015. Studying developmental neurotoxic effects of bisphenol A (BPA) using embryonic stem cells. J. Environ. Sci. 36, 173–177. http://dx.doi.org/10.1016/j.jes.2015.08.002.

Liao, C., Kannan, K., 2011. Widespread occurrence of bisphenol A in paper and paper products: implications for human exposure. Environ. Sci. Technol. 45 (21), 9372–9379. http://dx.doi.org/10.1021/es202507f.

Lin, Y., Sun, X., Qiu, L., Wei, J., Huang, Q., Fang, C., et al., 2013. Exposure to bisphenol A induces dysfunction of insulin secretion and apoptosis through the damage of mitochondria in rat insulinoma (INS-1) cells. Cell Death Dis. 4. http://dx.doi.org/10.1038/cddis.2012.206.

Linthout, S.V., Spillmann, F., Schultheiss, H.P., Tschope, C., 2011. Effects of mesenchymal stromal cells on diabetic cardiomyopathy. Curr. Pharm. Des. 17 (30), 3341–3347.

Logginidou, H., Ao, X., Russo, I., Henske, E.P., 2000. Frequent estrogen and progesterone receptor immunoreactivity in renal angiomyolipomas from women with pulmonary lymphangioleiomyomatosis. Chest 117 (1), 25–30. http://dx.doi.org/10.1378/chest.117.1.25.

Mahemuti, L., Chen, Q., Coughlan, M.C., Zhang, M., Florian, M., Mailloux, R.J., et al., 2016. Bisphenol A exposure alters release of immune and developmental modulators and expression of estrogen receptors in human fetal lung fibroblasts. J. Environ. Sci. 48, 11–23.

Marino, M., Galluzzo, P., Ascenzi, P., 2006. Estrogen signaling multiple pathways to impact gene transcription. Curr. Genomics 7 (8), 497–508.

Massaro, D., Massaro, G.D., 2004. Estrogen regulates pulmonary alveolar formation, loss, and regeneration in mice. 287 (6), L1154–L1159. http://dx.doi.org/10.1152/ajplung.00228.2004.

Massaro, D., Clerch, L.B., Massaro, G.D., 2007. Estrogen receptor-alpha regulates pulmonary alveolar loss and regeneration in female mice: morphometric and gene expression studies. Am. J. Physiol. Lung Cell Mol. Physiol. 293 (1), L222–L228. http://dx.doi.org/10.1152/ajplung.00384.2006.

Medoff, B.D., Sauty, A., Tager, A.M., Maclean, J.A., Smith, R.N., Mathew, A., et al., 2002. IFN-gamma-inducible protein 10 (CXCL10) contributes to airway hyperreactivity and airway inflammation in a mouse model of asthma. J. Immunol. 168 (10), 5278–5286.

Midoro-Horiuti, T., Tiwari, R., Watson, C.S., Goldblum, R.M., 2010. Maternal bisphenol A exposure promotes the development of experimental asthma in mouse pups. Environ. Health Perspect. 118 (2), 273–277. http://dx.doi.org/10.1289/ehp.0901259.

Mollerup, S., Jorgensen, K., Berge, G., Haugen, A., 2002. Expression of estrogen receptors alpha and beta in human lung tissue and cell lines. Lung Cancer 37 (2), 153–159.

NAEPP (National Asthma Education and Prevention Program), 2007. Expert Panel Report 3 (EPR-3): guidelines for the diagnosis and management of asthma—summary report 2007. J. Allergy Clin. Immunol. 120 (5 Suppl), S94–138. http://dx.doi.org/10.1016/j.jaci.2007.09.043.

Nakajima, Y., Goldblum, R.M., Midoro-Horiuti, T., 2012. Fetal exposure to bisphenol A as a risk factor for the development of childhood asthma: an animal model study. Environ. Health 11, 8. http://dx.doi.org/10.1186/1476-069X-11-8.

Neri, M., Virzi, G.M., Brocca, A., Garzotto, F., Kim, J.C., Ramponi, F., et al., 2015. In vitro cytotoxicity of bisphenol A in monocytes cell line. Blood Purif. 40 (2), 180–186. http://dx.doi.org/10.1159/000437039.

Nickel, N., Jonigk, D., Kempf, T., Bockmeyer, C.L., Maegel, L., Rische, J., et al., 2011. GDF-15 is abundantly expressed in plexiform lesions in patients with pulmonary arterial hypertension and affects proliferation and apoptosis of pulmonary endothelial cells. Respir. Res. 12, 62. http://dx.doi.org/10.1186/1465-9921-12-62.

Prossnitz, E.R., Arterburn, J.B., Sklar, L.A., 2007. GPR30: a G protein-coupled receptor for estrogen. Mol. Cell. Endocrinol. 265-266, 138–142. http://dx.doi.org/10.1016/j.mce.2006.12.010.

Rezg, R., El-Fazaa, S., Gharbi, N., Mornagui, B., 2014. Bisphenol A and human chronic diseases: current evidences, possible mechanisms, and future perspectives. Environ. Int. 64, 83–90. http://dx.doi.org/10.1016/j.envint.2013.12.007.

Rincon, M., Irvin, C.G., 2012. Role of IL-6 in asthma and other inflammatory pulmonary diseases. Int. J. Biol. Sci. 8 (9), 1281–1290. http://dx.doi.org/10.7150/ijbs.4874.

Robinson, L., Miller, R., 2015. The impact of bisphenol A and phthalates on allergy, asthma, and immune function: a review of latest findings. Curr. Environ. Health Rep. 2 (4), 379–387. http://dx.doi.org/10.1007/s40572-015-0066-8.

Royce, S.G., Cheng, V., Samuel, C.S., Tang, M.L.K., 2012. The regulation of fibrosis in airway remodeling in asthma. Mol. Cell. Endocrinol. 351 (2), 167–175. http://dx.doi.org/10.1016/j.mce.2012.01.007.

Rubin, B.S., 2011. Bisphenol A: an endocrine disruptor with widespread exposure and multiple effects. J. Steroid Biochem. Mol. Biol. 127 (1–2), 27–34. http://dx.doi.org/10.1016/j.jsbmb.2011.05.002.

Schober, A., Bottner, M., Strelau, J., Kinscherf, R., Bonaterra, G.A., Barth, M., et al., 2001. Expression of growth differentiation factor-15/ macrophage inhibitory cytokine-1 (GDF-15/MIC-1) in the perinatal, adult, and injured rat brain. J. Comp. Neurol. 439 (1), 32–45. http://dx.doi.org/10.1002/cne.1333.

Schonfelder, G., Wittfoht, W., Hopp, H., Talsness, C.E., Paul, M., Chahoud, I., 2002. Parent bisphenol A accumulation in the human maternal-fetal-placental unit. Environ. Health Perspect. 110 (11), A703–A707.

Seachrist, D.D., Bonk, K.W., Ho, S.-M., Prins, G.S., Soto, A.M., Keri, R.A., 2016. A review of the carcinogenic potential of bisphenol A. Reprod. Toxicol. 59, 167–182. http://dx.doi.org/10.1016/j.reprotox.2015.09.006.

Sheller, J.R., Polosukhin, V.V., Mitchell, D., Cheng, D.S., Peebles, R.S., Blackwell, T.S., 2009. Nuclear factor kappa B induction in airway epithelium increases lung inflammation in allergen-challenged mice. Exp. Lung Res. 35 (10), 883–895. http://dx.doi.org/10.3109/01902140903019710.

Shimoya, K., Taniguchi, T., Matsuzaki, N., Moriyama, A., Murata, Y., Kitajima, H., et al., 2000. Chorioamnionitis decreased incidence of respiratory distress syndrome by elevating fetal interleukin-6 serum concentration. Hum. Reprod. 15 (10), 2234–2240.

Spanier, A.J., Kahn, R.S., Kunselman, A.R., Schaefer, E.W., Hornung, R., Xu, Y.Y., et al., 2014. Bisphenol A exposure and the development of wheeze and lung function in children through age 5 years. JAMA Pediatr. 168 (12), 1131–1137.

Staples, C.A., Dorn, P.B., Klecka, G.M., O'Block, S.T., Harris, L.R., 1998. A review of the environmental fate, effects, and exposures of bisphenol A. Chemosphere 36 (10), 2149–2173.

Tak, P.P., Firestein, G.S., 2001. NF-kappaB: a key role in inflammatory diseases. J. Clin. Invest. 107 (1), 7–11. http://dx.doi.org/10.1172/JCI11830.

USFDA (United States Food and Drug Administration), 2014. Bisphenol A (BPA): use in food contact application. Available at: http://www.fda.gov/NewsEvents/PublicHealthFocus/ucm064437.htm#regulations (Accessed on August 30, 2016).

Valentino, R., D'Esposito, V., Passaretti, F., 2013. Bisphenol-A impairs insulin action and up-regulates inflammatory pathways in human subcutaneous adipocytes and 3 T3-L1 cells. PLoS One 8 (12). http://dx.doi.org/10.1371/journal.pone.0082099.

Valentino, R., D'Esposito, V., Ariemma, F., Cimmino, I., Beguinot, F., Formisano, P., 2016. Bisphenol A environmental exposure and the detrimental effects on human metabolic health: is it necessary to revise the risk assessment in vulnerable population? J. Endocrinol. Investig. 39 (3), 259–263. http://dx.doi.org/10.1007/s40618-015-0336-1.

Vandenberg, L.N., Hauser, R., Marcus, M., Olea, N., Welshons, W.V., 2007. Human exposure to bisphenol A (BPA). Reprod. Toxicol. 24 (2), 139–177. http://dx.doi.org/10.1016/j.reprotox.2007.07.010.

Vandenberg, L.N., Maffini, M.V., Sonnenschein, C., Rubin, B.S., Soto, A.M., 2009. Bisphenol-A and the great divide: a review of controversies in the field of endocrine disruption. Endocr. Rev. 30 (1), 75–95. http://dx.doi.org/10.1210/er.2008-0021.

Vandenberg, L.N., Chahoud, I., Heindel, J.J., Padmanabhan, V., Paumgartten, F.J.R., Schoenfelder, G., 2010. Urinary, circulating, and tissue biomonitoring studies indicate widespread exposure to bisphenol A. Environ. Health Perspect. 118 (8), 1055–1070. http://dx.doi.org/10.1289/ehp.0901716.

Wang, J., Xia, W., Xiao, Y.H., Ying, C.J., Long, J., Zhang, H., et al., 2014. Assessment of estrogen disrupting potency in animal foodstuffs of China by combined biological and chemical analyses. J. Environ. Sci. 26 (10), 2131–2137. http://dx.doi.org/10.1016/j.jes.2014.08.013.

Wetherill, Y.B., Akingbemi, B.T., Kanno, J., McLachlan, J.A., Nadal, A., Sonnenscheing, C., et al., 2007. In vitro molecular mechanisms of bisphenol A action. Reprod. Toxicol. 24 (2), 178–198. http://dx.doi.org/10.1016/j.reprotox.2007.05.010.

Xia, W., Jiang, Y., Li, Y., Wan, Y., Liu, J., Ma, Y., et al., 2014. Early-life exposure to bisphenol A induces liver injury in rats involvement of mitochondria-mediated apoptosis. PLoS One 9 (2), e90443. http://dx.doi.org/10.1371/journal.pone.0090443.

Yin, N.Y., Yao, X.L., Qin, Z.F., Wang, Y.L., Faiola, F., 2015. Assessment of bisphenol A (BPA) neurotoxicity *in vitro* with mouse embryonic stem cells. J. Environ. Sci. 36, 181–187. http://dx.doi.org/10.1016/j.jes.2015.06.004.

Zhang, K.S., Chen, H.Q., Chen, Y.S., Qiu, K.F., Zheng, X.B., Li, G.C., et al., 2014. Bisphenol A stimulates human lung cancer cell migration via upregulation of matrix metalloproteinases by GPER/EGFR/ERK1/2 signal pathway. Biomed. Pharmacother. 68 (8), 1037–1043. http://dx.doi.org/10.1016/j.biopha.2014.09.003.

Zimmers, T.A., Jin, X., Hsiao, E.C., McGrath, S.A., Esquela, A.F., Koniaris, L.G., 2005. Growth differentiation factor-15/macrophage inhibitory cytokine-1 induction after kidney and lung injury. Shock 23 (6), 543–548.