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Commentary: Exposure to High Endotoxin Concentration Increases Wheezing Prevalence Among Laboratory Animal Workers: A Cross-Sectional Study

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Endotoxins are an important structural component of the outer membrane of Gram-negative bacteria[1]. Its main component, lipopolysaccharide (LPS) is formed by the phosphoglycolipid lipid A that is covalently linked to hydrophilic heteropolysaccharide and accounts for its toxicity[2]. Endotoxin can be found in certain occupational settings such as those involving laboratory animals, livestock, fiberglass manufacturing, saw and cotton mills, waste management, grain and vegetable agriculture, as well as in house dust[3].

The study by Freitas et al. (2016)[4] was aimed at a better understanding of the effects of endotoxin exposure. There are studies showing benefits and others showing harmful effects. Understanding the effects of exposure to endotoxin among workers exposed to laboratory animals is of great importance because it is a group with high risk for several health impairments. Among the risks, we can mention a high prevalence of sensitization to laboratory animals[5,6]. Once sensitized to laboratory animals, these workers are at high risk for asthma, bronchial hyperresponsiveness and rhinitis[7]. Thus, understanding the effects of exposure to endotoxin among workers exposed to laboratory animals may help inform preventive measures.

In our study, we have analyzed data of 751 workers, of these, 412 individuals were exposed to laboratory animals, called exposed group and 339 individuals were not exposed to laboratory animals, called non-exposed group. In addition, 145 samples of dust were collected from the workplace of those 751 workers; 92 samples from the exposed group and 53 samples from the non-exposed group. The median endotoxin concentration of the 145 samples was 20.4 EU/mg of dust.

We observed that the median endotoxin concentration in the exposed group was 34.2 EU/mg, whereas in the non-exposed group the median was 10.2 EU/mg, $p < 0.001$. These results show the strong relationship between animal presence and concentration of endotoxin, since with presence of laboratory animals was associated with an average 3-fold increase in endotoxin concentration. Among the non-exposed workplaces, 36% had endotoxin concentrations above 20.4 EU/mg of dust; whereas in the exposed group workplaces, 66% had concentrations above 20.4 EU/mg of dust.

We observed that individuals exposed to concentrations greater than 20.4 EU/mg of dust were more likely to report wheezing in the

last 12 months (self-report) when compared to individuals exposed to lower concentrations. In addition, when endotoxin concentrations were categorized into quartiles, we observed that prevalence of wheezing among workers exposed to laboratory animals increased as endotoxin concentrations increased. Such a pattern of increased wheezing prevalence was not observed among workers non-exposed to laboratory animals. The prevalence of asthma (defined by the presence of symptoms detected by questionnaire and bronchial hyperresponsiveness detected by bronchial challenge test) was not affected by exposure to low or high concentrations of endotoxin.

We showed that laboratories with small rodents (rat, rabbit, mouse, hamster, or guinea-pig) bear high concentrations of endotoxin; previous studies show that low concentrations of endotoxin can also be found in these laboratories. Oppliger et al (2017)[8] classified workers according to their jobs and observed that researchers were exposed to a median daily concentration of 0.83 EU/m^3 and various other jobs with exposure to animal were exposed to median daily concentrations of 2.97 EU/m^3.

The effects of exposure to low concentrations of endotoxin are still unclear. A systematic review showed that even low levels of airborne endotoxin (< 100 EU/m^3) seem plausible to induce respiratory health effects[9]. While in an experimental study, mice exposed for two weeks at low doses of endotoxin (100 ng) had reduced IL-5 and IL-13 production, with no signs of asthma[10].

Exposure to high concentrations of endotoxin have different consequences for groups of workers, according to their atopic status. Atopic workers exposed to high concentrations of endotoxin had an increased risk for upper (sneezing and runny nose) and lower (cough, wheezing, and chest tightness) airway symptoms, while non-atopic workers had a low risk for such symptoms[11]. In addition, atopic subjects were divided into two groups, CD14/-1619 G allele and CD14/-1619 AA allele. The first showed reduced FEV1 and FEF25-75%, as compared with the second group (CD14/-1619 AA allele), this is evidence of the gene-environment interaction that affects lung function in laboratory animal workers. Analyzing cumulative exposure to endotoxin, based on the task performed and time spent to perform the task is a very interesting approach that seems to be the most accurate evaluation of exposure. This has been used by Pacheco et al. (2010)[12]. We have not employed this method. The single measurement of endotoxin in dust that we have adopted could be considered a weakness of our study.

Based on data available in scientific literature, exposures to both high and low concentrations of endotoxin are able to induce symptoms (such as wheezing[4,9], chest tightness, shortness of breath, and cough[9]), which leads to the need for measures aimed at reducing exposure to endotoxins. Platts-Mills et al. (2005)[13] showed that the levels of endotoxin in all laboratories with filter cage tops were reduced by 95%, when compared from those from laboratories with open cages. In some laboratories, the reduction was over 99%. In addition, endotoxin concentrations are altered by laboratory illumination and temperature, where the higher the illumination and temperature, the lower the endotoxin concentration[14].

Among other groups exposed to endotoxins, the results are conflicting. In a farming population, the geometric mean concentration of endotoxin in dust samples collected from the bed and bedroom was 30.4 EU/mg. Increased endotoxin concentration was associated with increased risk for current asthma[15]. Different results were presented by Eduard et al. (2004)[16] who demonstrated that, among farmers, exposure to higher concentration of airborne endotoxin during work was a protective factor for atopic asthma. In addition, exposure to endotoxin may alter the risk for sensitization. For instance, a 15-year follow-up study showed that increased exposure to endotoxin was associated with reduced new sensitization to pollen[17].

One limitation of our study is that it is a cross-sectional study, so we do not know the impact of prolonged exposure to high concentrations of endotoxin. Although the endotoxin concentration was not associated with an increase in the prevalence of asthma, it was associated with an increase in wheezing. Wheezing is due to the narrowing of the airways, commonly observed in asthmatic people. Individuals with intermittent asthma may report wheezing without constant bronchial hyperreactivity. In this case, bronchial hyperreactivity would not be detected on the day of examination. In this scenario, perhaps prolonged exposure to high concentrations of endotoxin could induce a progression of symptoms and workers may eventually develop persistent asthma.

In conclusion, further studies on the effects of endotoxin exposure are needed, especially studies investigating the mechanisms that trigger symptoms related to endotoxin exposure. Contrary to some studies demonstrating the beneficial effect of endotoxin exposure among specific groups, exposure to endotoxin among laboratory animal workers seems to induce asthma symptoms. If further research confirms that endotoxins have detrimental effects, measures aimed at reduction exposure to endotoxin should be employed, such as replacement of open cages with ventilated cages with filters, and control of temperature and illumination.

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