

Health Update: Influence of Genetic Variants on Ozone Responses of Asthmatic Children

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California Air Resources Board

California Environmental Protection Agency

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Thank you Ms. Witherspoon. Good morning Dr. Sawyer and members of the Board.

Staff has often spoken to you about the considerable body of scientific literature indicating that ozone exposure can induce adverse health impacts, such as reduced lung function, respiratory symptoms, hospitalization and emergency room visits, but staff has not told you about how the body defends itself from injury due to air pollution exposure.

The paper we are presenting this morning is by Romieu et al., and is entitled “GSTM1 and GSTP1 and respiratory health in asthmatic children exposed to ozone.” It appeared in the European Respiratory Journal in late 2006. The authors are associated with the National Institute of Public Health in Cuernavaca, Mexico, the Federico Gomez Children’s Hospital in Mexico City, and the US National Institute of Environmental Health Sciences. The paper describes the results of a study of asthmatic children living in Mexico City, and the influence of differences in two genes that are involved in defending the body from ozone-induced injury.

Full citation: Romieu, I, M Ramirez-Aguilar, JJ Sienra-Monge, H Moreno-Macias, B E del Rio-Navarro, G. David, J Marzec, M Hernandez-Avila, SJ London. *GSTM1* and *GSTP1* and respiratory health in asthmatic children exposed to ozone. *Eur Resp J.* 28:953-959, 2006.

Background

- Responsiveness to ozone varies widely
- Key question
 - Why are some people more affected than others?
- Gene-based differences may explain Children's Health Study results
 - Genetic differences influence susceptibility to
 - Environmental tobacco smoke
 - Frequency of acute respiratory illnesses

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It is well known that there is considerable variability in responsiveness to ozone, and that people with asthma and other lung diseases have responses that fall into the same range as healthy people.

This being said, people with compromised baseline lung function, for example due to asthma or other chronic lung disease, are at increased risk, because their response to ozone is superimposed on top of reduced baseline status.

A key unanswered question has been why are some people more susceptible to adverse responses with environmental exposure than others?

Research has only recently begun to address this question. Recent findings from The Children's Health Study and several other laboratories point to a role for genetic differences in lung defense mechanisms in explaining inter-individual differences in susceptibility to environmental tobacco smoke, and frequency of respiratory illness. Several researchers have also begun to investigate the role of genetic differences in susceptibility to ozone-induced effects.

Defense Against Ozone

- Ozone: a strong oxidant
- Specific enzymes defend against oxidative stress
 - GSTM1*
 - Variant type: inactive enzyme
 - GSTP1**
 - Variant type: less active enzyme

*Glutathione S-transferase M1,

**Glutathione S-transferase P1

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Chemically, ozone is a strong oxidant, and it reacts with the fluid and cells lining the airways, causing injury to the lung tissues.

One of the lung's defense mechanisms involves enzymes that counteracts the effects of oxidants. Two of these enzymes are glutathione S-transferase M1, produced by the gene GSTM1, and glutathione S-transferase P1, produced by the gene GSTP1. Each of these genes has two forms. The more common form produces active enzymes. But both of the genes has a common alternate or variant form. The variant type of GSTM1 gene produces an inactive enzyme that has no defensive properties. The variant type of the GSTP1 gene produces an an enzyme with less active defense properties.

So, we would expect that people who have the inactive type of GSTM1 gene or the inactive type of the GSTP1 gene would be more susceptible to ozone because they have less effective defenses against oxidant injury.

Methods

- Study
 - 151 asthmatic children (mild to severe)
 - Mexico City
 - Tested for type of GSTM1 and GSTP1
 - 12 week follow-up
- Symptom endpoints
 - Daily respiratory symptoms
 - Inhaler use (bronchodilator)
 - Lung function

Romieu et al. GSTM1 and GSTP1 and respiratory health in asthmatic children exposed to ozone. *Eur. Respir. J.* 28: 953-959, 2006.

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The study we are presenting this morning involved 151 asthmatic children who lived in Mexico City. Asthma severity ranged from mild to severe, although most of the children fell in the mild to moderate range.

Each child was tested for type of GSTM1 and GSTP1, and was followed for 12 weeks. The children's parents kept a daily diary of respiratory symptoms and bronchodilator inhaler use, and the children performed lung function tests twice a week at a clinic.

Single Gene Effects

- Active forms of GSTM1 and GSTP1
 - No associations with ozone
- Inactive form of GSTM1 associated with
 - Difficulty breathing
- Less active form of GSTP1 associated with
 - Cough
 - Difficulty breathing
 - Inhaler use

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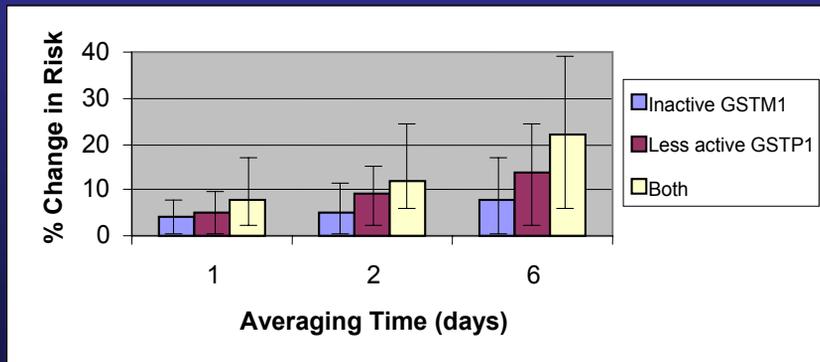
The results showed that for children with the **active** forms of GSTM1 and GSTP1 there were no associations between ambient ozone and cough, breathing difficulty, or bronchodilator use. This suggests that people who have the active forms of these two genes are protected against adverse effects related to ozone exposure.

However, for children with the inactive form of GSTM1, ozone was significantly associated with breathing difficulty, whether exposure was on the previous day, or was an average of the previous two or six days.

In children with the less active form of GSTP1, ozone exposure was associated with cough, difficulty breathing and bronchodilator use, particularly when exposure was averaged over several previous days.

Combined Gene Effect

- Children with both inactive form of GSTM1 and less active form of GSTP1
 - Greatest risk of breathing difficulty

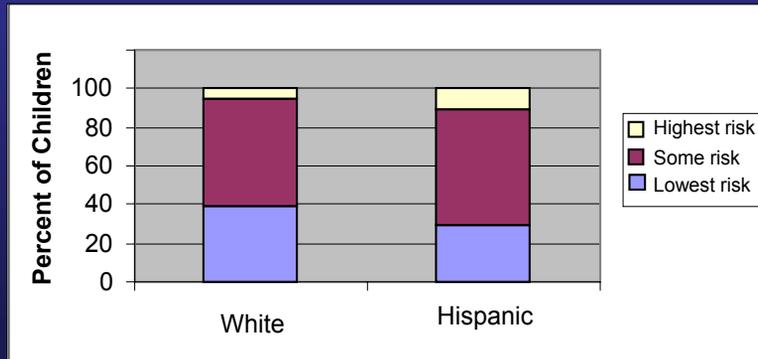


20 ppb change in 1-hr maximum ozone concentration

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As you can see from this figure, children who had **both** the inactive form of GSTM1 and the less active form of GSTP1 (shown in the yellow bar) had the greatest risk of experiencing difficulty breathing with ozone exposure, compared to children having only the inactive form of GSTM1 or the less active form of GSTP1. In addition, as you can see from the slide, risk of experiencing breathing difficulty increased as the ozone averaging time lengthened from one, to two and six previous days. In addition, as you can see in the chart, the trend in risk associated with having both alternate gene forms was greater than that observed for children who had only one of the inactive variants.

Distribution of Gene Types and Risk in Children*



*Data from Children's Health Study cohort

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You may be wondering how many people have the GSTM1 and GSTP1 types associated with greater risk of ozone-related symptoms. This slide shows the percentage of white and Hispanic children in one of the Children's Health Study cohorts who had the active forms of both genes, in blue, the inactive form of GSTM1 or the less active form of GSTP1, in burgandy, and both the inactive form of GSTM1 and the less active form of GSTP1, in yellow. For comparison, 38% of the children in the study we are presenting today had the inactive form of GSTM1, while 36% had the less active form of GSTP1, and 14% had both.

Conclusions

- Genetics influences susceptibility to ozone
- Implications
 - Need to reconsider how we think about susceptibility to air pollution
 - Susceptibility includes more than baseline health status
- Ongoing research
 - ARB-funded study at U.C. San Francisco
 - Additional studies in Mexico City

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These results suggest that genetics plays a role in sensitivity to ozone, and that asthmatics, and likely non-asthmatics as well, who have genetic variants that provide less effective defenses are at increased risk of experiencing adverse effects when exposed to ozone.

This implies that we may need to reconsider how we think about susceptibility to air pollution, because these results, and those from other studies suggest that susceptibility incorporates more than just baseline health status, for example whether or not a person has a chronic health problem, such as asthma.

The results discussed today begin to address the question of how ozone harms human health. The Board is also concerned with this fundamental question and is currently funding a controlled human exposure study investigating the influence of variants in GSTM1 and GSTP1 on ozone-induced responses of adult asthmatics. The authors of the paper presented this morning are continuing to investigate the influence of these variants, as are other investigators. In addition several researchers are beginning to look at the roles of several other gene variants to susceptibility to ozone-induced health effects.

Thank you for your attention. We would be pleased to answer any questions you may have.