How do combustion related products cause/induce asthma and what can we do about it?

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Science Questions

Exposure to Combustion Related Products (CRPs) such as diesel exhaust and secondary atmospheric products such as ozone have been implicated by human and animal studies to worsen asthma. There is accumulating evidence that they may also have a role in asthma development. Our inter-disciplinary program has therefore focused on these key questions:

What are the key combustion related products responsible for inducing/exacerbating asthma?

What are the key pathways by which combustion related products affect asthma?

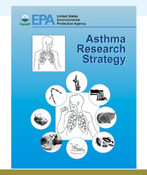
Who is at increased risk and how can interventions be used to reduce the burden of asthma from combustion related products?

Research Goals

Asthma is an environmental disease with a huge health, economic and societal burden. It affects over 20 million Americans and is estimated to cost nearly $18 billion and account for more than 14 million school days per year annually. Asthmatics and especially children appear to be be more sensitive to the adverse health effects of air pollutants.

The research goals of this program are therefore centered on:

1. Identifying individual components or defined mixtures that produce health effects in asthmatics
2. Understanding upstream pathways and susceptibility factors that may predict those who will be at increased risk
3. Developing methods to minimize risk.



US EPA ARCHIVE DOCUMENT

Findings and Conclusions

Traffic is a major source of CRPs that exacerbate asthma.
Two major epidemiology studies performed in two urban areas Detroit and in S. California suggest traffic can impact clinical endpoints of asthma.
In Detroit elevated eosinophils are associated with traffic intensity for those living close to a freeway.
Similarly in S. California children living close to a freeway show decreased lung function.
Exposure to traffic and PM2.5 can override the protective effects of high lung function and increase incident asthma rates.

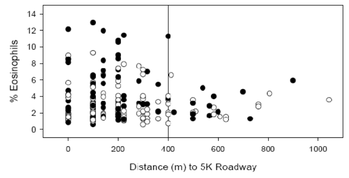
Diesel exhaust, an important component of traffic, induces inflammation and promotes allergic responses.
There are distinct gene and pathway responses between different diesel particles and between species.
However, we have identified 4 toxicological pathways (metabolism, apoptosis, cell cycle control, and inflammation) in common between particles and models.
A novel process has been identified that may regulate diesel effects on allergic asthma through epigenetic modifications.

A subgroup of asthmatics may acquire increased sensitivity to aeroallergens after exposure to ozone
Ozone exposure will increase antigen presentation markers in the human airway. Similarly, diesel particles can activate dendritic cells in vitro and in mouse models.
CRPs may also enhance responses to viruses a key trigger of asthma by altering the innate immune response.
Anti-oxidant genes such as GSTM1 and EPHX1can modify asthma risk, this in turn is modified by traffic exposure.

GSTM1 is a protective factor for the pro-allergic and pro-inflammatory effects of diesel particles
Recruitment of inflammatory cells following ozone exposure is modified by GSTM1
Exogenous or induction of endogenous anti-oxidants can reduce lung injury and inflammation by CRPs in vitro and in animal asthma models
Endogenous anti-oxidants can be induced in the airway of human subjects by dietary interventions

Methods/Approach

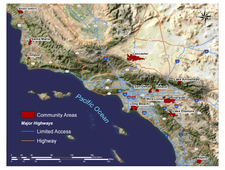
Detroit Children's Health Study



Monitoring and clinical endpoints (black circles are asthmatic, open circles are non-asthmatic children).

We identified a case-cohort sample of 6,883 children aged 7-12 years at time of recruitment, in the greater Detroit metropolitan area (Detroit and Dearborn, Michigan) through the Henry Ford Health System. The resulting sample of 1,157 completed questionnaires included 327 asthmatic and 830 non-asthmatic children with residential estimates of ambient exposure from land use regression models. At the next level, 705 children completed clinical examinations of lung function and exhaled breath. Eosinophil levels (an effector and indicator of allergic asthma status) were significantly elevated in asthmatic children living close to the freeway.

S. California Children's Health Study

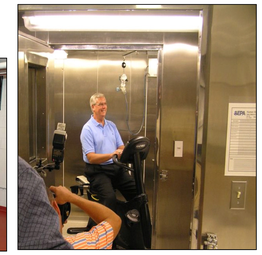


Freeway Regional $PM_{2.5}$	Distance to >1,500m	<500m
Low		Best -80 ml
High		-100 ml -180 ml

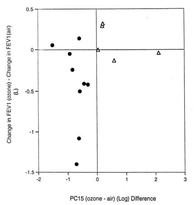
Estimated deficits in 8-yr FEV1 growth, relative to living >1,500m from a freeway inthe lowest $PM_{2.5}$ community

In a prospective study, 3677 children (mean age 10 years [SD 0.44]) participated from 12 southern California communities that represent a wide range in regional air quality. Children were followed up for 8 years, with yearly lung-function measurements recorded. For each child, we identified several indicators of residential exposure to traffic from large roads. Regression analysis established that children who lived within 500 m of a freeway (motorway) had substantial deficits in 8-year growth of forced expiratory volume in 1 s (FEV(1), and maximum midexpiratory flow rate, compared with children who lived at least 1500 m from a freeway. The effects of freeway proximity to residences similar to and independent of effects of regional pollution

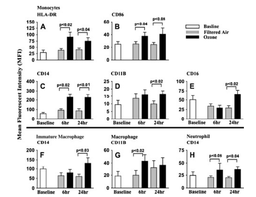
In vivo exposure studies



An integrated program utilizing animal and human inhalation facilities have studied the effect of various CRPs in the upper and lower airways. Human studies have compared asthmatic, allergic and healthy subjects after acute exposure, while complementary animal models of asthma have also enabled investigation of longer term exposures.



Fourteen subjects were exposed to 0.2 ppm O3 or filtered air. After each exposure, the subjects were challenged with doubling doses of dust mite allergen. A subset (Group A) were more sensitive to allergen after ozone exposure compared to after air.

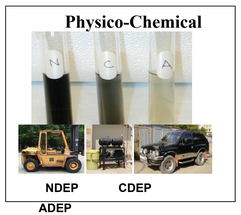


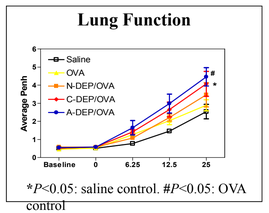
Ozone challenge enhances markers of innate immunity and antigen presentation on airway monocytes in healthy individuals providing a mechanism to explain adjuvant effects of CRPs.

	GSTM1		
	Null (n=14)	Present (n=5)	p
IgE			
Clean air and allergen	6·9 (2·6–24·3)	8·9 (4·3–18·8)	0·40
DEP and allergen	106·6 (8·8–534·8)	49·8 (14·2–79·4)	0·15
Difference	102·5 (1·0–510·5)	45·5 (–1·5–60·6)	0·03
Histamine			
Clean air and allergen	2·9 (1·3–5·9)	2·8 (1·9–6·7)	0·96
DEP and allergen	16·9 (2·9–27·6)	9·8 (3·1–19·0)	0·08
Difference	14·0 (–0·2–24·7)	7·4 (1·2–12·3)	0·02

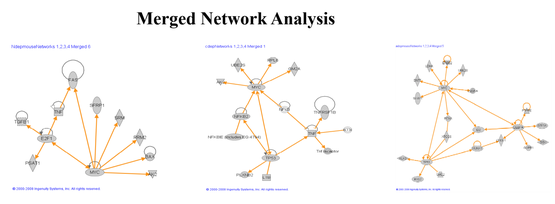
Exposure studies have built on associations observed in epidemiology studies to confirm that allergic and asthmatic individuals with reduced endogenous antioxidants such as those with GSTM1 deletion ('null' genotype) have greater allergic and inflammatory responses to CRPs.

Identifying common pathways determining CRP effects in airway inflammation





*P<0.05: saline control. #P<0.05: OVA control



The adjuvancy effect of three different diesel particles, NIST SRM 2975 (NDEP) generated from a heavy forklift, from a diesel engine used to power a compressor (CDEP), and an automobile (ADEP), were assessed in a murine allergic asthma model after challenge. Gene expression changes were analyzed 18 hrs post-sensitization to identify pathways responsible for this effect. While all induced some degree of adjuvancy, there was a marked difference in potency C-DEP > ADEP >> NDEP. However, there were 236 significantly altered genes that were common to all DEP/OVA treatments and network analysis reveled 4 unifying processes These same 4 pathways were found in human bronchial epithelial cells stimulated with diesel particles.

Impact and Outcomes

Results used by National Asthma Education and Prevention Program (NAEPP) Guidelines to support recommendation that clinicians advise patients to avoid exertion outdoors when levels of air pollution are high
http://www.nhlbi.nih.gov/guidelines/asthma/asthgdln.htm

Results have been used in criteria documents and for standard setting of various air pollutants
http://cfpub.epa.gov/ncea

Information is used by the Office of Air and Radiation and the Office of Transportation and Air Quality for hazard identification and risk /benefit assessment.

Results used by local governments and various community groups to inform and impact decisions on issues of health consequences of urban growth such as expansion of the Los Angeles and San Pedro ports

Future Directions

•Identifying the basis of genetic susceptibility in asthmatics to CRPs.
•Understanding the role of asthma severity on the health impacts of CRPs.
•Using results of gene profiling and a systems approach to identify common pathways of effects in asthmatics and relative potencies of different CRPs.
•Use of computational models to predict total health burden on asthmatics in ambient air sheds.
•Identifying subtypes of asthma with increased susceptibility to CRPs.
•Identifying the role of epigenetic regulation in determining susceptibility of asthmatics to CRPs.
•Clarify whether asthmatics have increased susceptibility to cardiac and other non-asthma health effects of CRPs
•Identify appropriate intervention strategies to mitigate the effects of CRPs in asthmatics

Researchers Involved

Robert Devlin, David Diaz-Sanchez, Jane Gallagher, Ian Gilmour, Lucas Neas, Ana Rappold , Tina Stevens (NHEERL) Ronald Williams (NERL), Frank Gilliland, Rob McConnell (University of Southern California) Steven Georas (Johns Hopkins University), Rachel Miller (Columbia University)

Susceptible Populations