Slide 1

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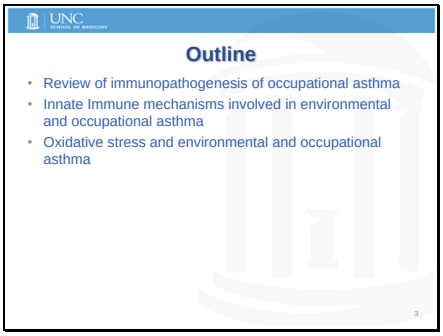
Slide 3



Slide 4

Sensitization to occupational allergens

HMW vs. LMW sensitizers

Reference:

Dykewicz MS.

J Allergy Clin Immunol. 2009 Mar;123(3):519-28;

4

Slide 5

High Molecular Weight Allergens

- Immunopathology typically due to IgE production to high molecular weight allergens
- Airway inflammation is typically eosinophilic
- Occupational sensitization to a given agent may be due to different allergens compared to other allergy associated with the same agent
  - Bakers asthma associated exposure to agents such as thioredoxins in wheat
  - Oral allergy due to wheat associated with omega 5 gliadin

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Slide 6

High molecular weight allergens

Agent	Industry, process, or occupation
High molecular weight	
Animal and insect–derived	
Bird proteins (feathers, serum)	Bird breeders
Crustaceans: snow crab, prawn	Seafood processors
Eggs (chicken)	Food processors
Insects	Beekeepers, farmers, granary workers, silk processing, dockworkers
Mammalian proteins in hair, dander, urine	Research labs, veterinarians, breeders, pet shop workers
Pharmaceutical enzymes, eg, pancrease	Pharmaceutical industry, health-care workers
Sea squirt (oyster parasite)	Oyster processing workers
Bacterial and fungal–derived	
Bacillus subtilis–derived enzymes	Detergent formulators
Penicillium casei	Cheese workers
Thermophilic molds	Mushroom workers
Plant-derived	
Henna dye	Beauticians
Latex, natural rubber	Health care workers
Plant enzymes (papain, bromelain)	Food, pharmaceutical industries
Psyllium	Laxative manufacture, nursing
Vegetable gums (arabic, guar, tragacanth)	Printing/bookbinders, food, carpet manufacture
Wheat flour	Bakers

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Low molecular weight sensitizers

- Some cause disease via IgE mediated mechanisms
  - Phthalic anhydride
  - TMA
  - Chromium salts
  - Nickle salts
  - Epoxy amines
  - Penicillin
- Others involve mechanisms which are incompletely understood
  - Innate mechanisms
  - Cell mediated mechanisms
  - Isocyanates may have multiple mechanisms

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Low molecular weight allergens

Low molecular weight	
Persulfates (in hair bleaching solutions)	Hairdressers
Metals and metal salts	
Chromium	Miners and cement, electroplating and tanning workers
Cobalt	Metal workers and diamond polishers
Nickel sulfate	Metal plating
Platinum	Alloy makers
Organic chemicals	
Acid anhydrides (prototype: trimellitic anhydride)	Plastics industry, dye, insecticide makers, organic chemical manufacture (used in epoxy resins)
Acrylates, methacrylate (artificial nail glue)	Printing industry, beauticians
Ethylenediamine	Shellac-lacquer industry workers
Paraphenyldiamine in hair dye	Hairdressers
Polyisocyanates (prototype: toluene diisocyanate)	Polyurethane, foam coatings, adhesives production, and end-use settings (e.g, spray painters, foam workers)
Pharmaceuticals (antibiotics, cimetidine)	Hospital and pharmaceutical workers

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Slide 9

Irritant-induced asthma

- Often linked to a single initial event
- Often not IgE mediated
- Likely involves epithelial cell injury
- Increased methacholine reactivity
- Traditionally called RADs

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Slide 10

New areas of investigation for OA

- Can we extrapolate lessons from the “hygeine hypothesis”?
- Can we extrapolate lessons from the biology of environmental/air pollution research to the unique exposures of OA?
- Specific interest in oxidative stress?

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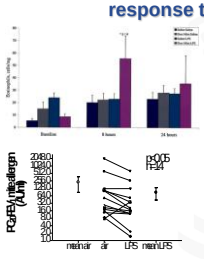
Slide 11

Innate Immunity and OA

Animal handlers

Slide 12

Pollutants shown to enhance recall response to allergen



- Ozone
- NO_2/SO_2
- Endotoxin
- Diesel Exhaust
- ETS
- Responses include:
  - IgE
  - PMNs
  - Eosinophils
  - Airway Reactivity

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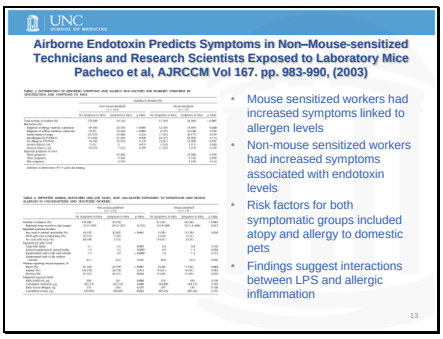

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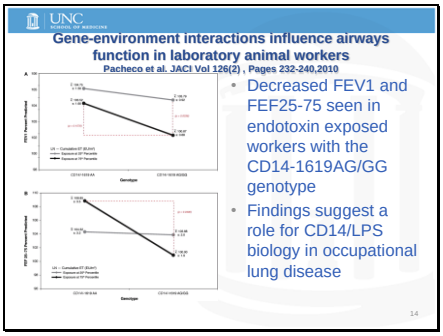

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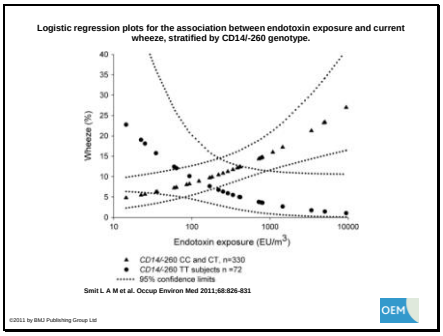

Logistic regression plots for the association between endotoxin exposure and current wheeze, stratified by CD14/-260 genotype. Each symbol represents a group of workers with the same estimated exposure level. Associations were adjusted for sex, age, smoking habits and farm childhood.

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Hexamethylene diisocyanate asthma is associated with genetic polymorphisms of CD14, IL-13, and IL-4 receptor α

Bernstein D, et al, JACI 128(2), Pages 418-420, 2011

TABLE I. Logistic regression analyses of associations of genotype or genotype combinations and exposure (HDI vs MDI and/or TDI) with occupational asthma confirmed by SIC-positive (DA$^+$) versus SIC-negative (DA$^-$) workers in all diisocyanate-exposed workers (**A**), and of genotype or genotype combinations with DA$^+$ versus DA$^-$ in HDI-exposed workers (**B**), after adjusting for significant demographic characteristics

Genotype or genotype combinations of *IL4RA* (I50V), *IL13* (R130Q), and *CD14* (C159T) SNPs	*P* values: Genotype or genotype combination main effect	Exposure main effect, HDI vs MDI, TDI	Genotype or genotype combination by exposure interaction	OR (95% CI) for genotype among diisocyanate-exposed workers
A. All workers				
IL4RA II*	.810	.0001	.300	1.57 (0.74–3.32)†
IL4RA II and *IL13* RR	.578	.003	.051	1.66 (0.66–4.17)†
IL4RA II and *CD14* CT	.895	.033	.006	2.86 (1.25–7.08)†
IL4RA II and *IL13* RR and *CD14* CT	.801	.566	.005	5.55 (1.19–30.55)‡
B. HDI workers only				
IL4RA II	.292			1.51 (0.70–3.28)†
IL4RA II and *IL13* RR	.360			1.56 (0.62–4.06)†
IL4RA II and *CD14* CT	.015			3.08 (1.25–7.60)†
IL4RA and *IL13* RR and *CD14* CT	.019			3.86 (1.26–11.80)‡

OR, Odds ratio.

*Each row represents a separate logistic model. Genotypes are dichotomized so that *IL4RA* II comparies the II genotype to the IV/or VV genotypes, *IL13* compares the RR genotype to the RQ or QQ genotypes, and *CD14* CT compares the CT genotype to the CC or TT genotype. Combinations of genotypes seen pare be indicated SNP constitution with all others combinations. For example, *IL4RA* II and *IL13* RR compare the combination of *IL4RA* (I50V) = II and *IL13* (R130Q) = RR with all other combinations of *IL4RA* (I50V) and *IL13* (R130Q).

†Adjusted for smoking.

‡Adjusted for smoking and ethnicity.

§Adjusted for smoking and sex.

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Interim summary: innate immunity

- Innate immunity results in:
  - Increased antigen presentation capability
  - Increased inflammation
- Innate immunity (CD14) influences symptoms and risk of disease
  - Bioaerosols
  - Event TDI
- Gene X exposure
  - CD14 TT genotype increased wheeze at low LPS
  - Decreased wheeze at high LPS
  - CD14 CC or CT associated with wheeze with high LPS

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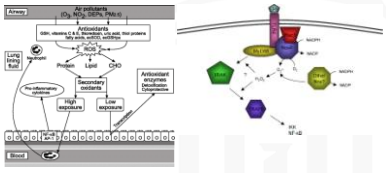
Oxidant Biology and Inflammation



- **Multiple environmental pollutants are oxidant or pro-oxidant molecules (Romieu et al 2008)**
- **Native oxidant generation plays an important role in immune response (Gaudie et al, 2006)**

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GSTM1 and related genes

NRF2 nuclear transcription factor

- Epidemiological literature too extensive to review here. In summary, GSTM1 null individuals have increased risk for:
  - Ozone induced asthma exacerbation
  - PM induced lung and CV disease
  - Perinatal exposure to tobacco smoke and increased risk of asthma/wheezing disease
  - Associated with increased risk for isocyanate asthma and response to LPD
- GSTM1 Null challenge studies:
  - Associated with increased response to diesel exhaust
  - Associated with increased response to tobacco smoke

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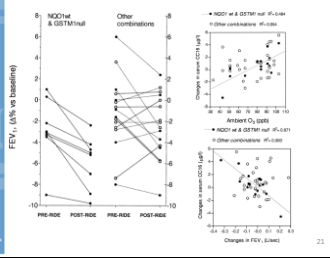
GSTM1 genotype and ozone response

Lung Function
Inflammation

Slide 21

Polymorphism of Quinone-metabolizing Enzymes and Susceptibility to Ozone-induced Acute Effects

Bermagashi, et al Am. J. Respir. Crit. Care Med., Volume 163, Number 6, May 2001, 1426-1431



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Effect of GSTM1 genotype and ozone induced decreases in FEF25-75 in asthmatics

Romieu et al, Thorax 2004;59:8-10

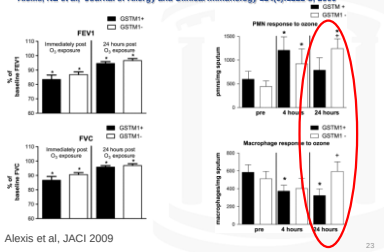
- GSTM1 null asthmatics have increased asthma symptoms with ozone exposure than do GSTM1 sufficient persons

		All asthmatics			Moderate and severe asthmatics		
Group	Subgroup	n*	Coefficient [95% CI]†, ml/s 50 ppb O_3	Percentage [95% CI] change‡ FEF_{25-75}/50 ppb O_3	n	Coefficient [95% CI], ml/s 50 ppb O_3	Percentage [95% CI] change FEF_{25-75}/50 ppb O_3
Placebo	GSTM1 null	29	−50.5 [−90.1 to −10.9]§	−2.9 [−5.2 to −0.6]§	18	−80.8 [−132.7 to −28.9]§	−4.7 [−7.7 to −1.7]§
	GSTM1 positive	49	−10.5 [−38.7 to 17.7]	−0.6 [−2.1 to 0.9]	17	−34.4 [−75.6 to 6.8]	−1.9 [−4.4 to 0.5]
	Genotype effect		40.0 [−7.5 to 87.5]¶	2.3 [−0.2 to 4.9]¶		46.4 [−20.7 to 113.4]	2.8 [−1.2 to 6.7]

Slide 23

The glutathione-S-transferase Mu 1 null genotype modulates ozone-induced airway inflammation in human subjects

Alexis, NE et al, Journal of Allergy and Clinical Immunology 124(6):1222-8; 2009



Alexis et al, JACI 2009

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GSTM1 genotype and PM response

Lung Function
Inflammation

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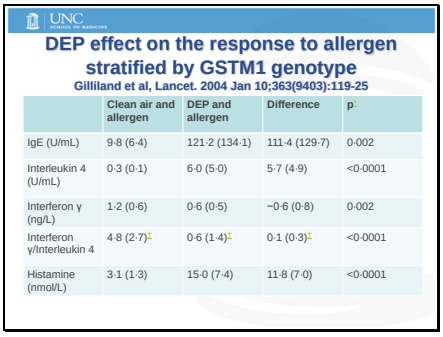

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DEP effect on the response to allergen stratified by GSTM1 genotype

Gilliland et al, Lancet. 2004 Jan 10;363(9403):119-25

	Clean air and allergen	DEP and allergen	Difference	p*
IgE (U/mL)	9·8 (6·4)	121·2 (134·1)	111·4 (129·7)	0·002
Interleukin 4 (U/mL)	0·3 (0·1)	6·0 (5·0)	5·7 (4·9)	<0·0001
Interferon γ (ng/L)	1·2 (0·6)	0·6 (0·5)	−0·6 (0·8)	0·002
Interferon γ/Interleukin 4	4·8 (2·7)†	0·6 (1·4)†	0·1 (0·3)†	<0·0001
Histamine (nmol/L)	3·1 (1·3)	15·0 (7·4)	11·8 (7·0)	<0·0001

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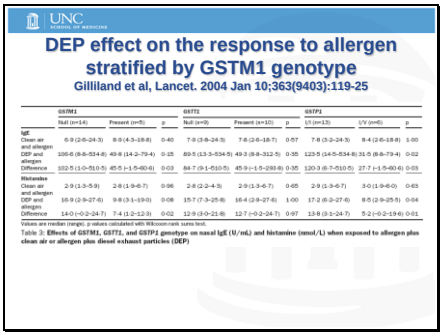

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DEP effect on the response to allergen stratified by GSTM1 genotype

Gilliland et al, Lancet. 2004 Jan 10;363(9403):119-25

	GSTM1			GSTT1			GSTP1		
	Null (n=14)	Present (n=5)	p	Null (n=9)	Present (n=10)	p	I/I (n=13)	I/V (n=6)	p
IgE									
Clean air and allergen	6·9 (2·6–24·3)	8·9 (4·3–18·8)	0·40	7·9 (3·8–24·3)	7·6 (2·6–18·7)	0·57	7·8 (3·2–24·3)	8·4 (2·6–18·8)	1·00
DEP and allergen	106·6 (8·6–534·6)	49·8 (14·2–79·4)	0·15	89·5 (13·3–534·5)	49·3 (8·6–312·5)	0·35	123·5 (14·5–534·6)	31·5 (8·6–79·4)	0·02
Difference	102·5 (1·0–510·5)	45·5 (–1·5–80·6)	0·03	84·7 (0·1–510·5)	45·9 (–1·5–289·8)	0·35	120·3 (6·7–510·5)	27·7 (–1·5–80·6)	0·03
Histamine									
Clean air and allergen	2·9 (1·3–5·9)	2·8 (1·9–6·7)	0·96	2·8 (2·2–4·3)	2·9 (1·3–6·7)	0·65	2·9 (1·3–6·7)	3·0 (1·9–6·0)	0·63
DEP and allergen	16·9 (2·9–27·6)	9·8 (3·1–19·0)	0·08	15·7 (7·3–25·8)	16·4 (2·9–27·6)	1·00	17·2 (6·2–27·6)	8·5 (2·9–25·5)	0·04
Difference	14·0 (–0·2–24·7)	7·4 (1·2–12·3)	0·02	12·9 (3·0–21·8)	12·7 (–0·2–24·7)	0·97	13·8 (3·1–24·7)	5·2 (–0·2–19·6)	0·01

Values are median (range). p values calculated with Wilcoxon rank sums test.

Table 3: **Effects of GSTM1, GSTT1, and GSTP1 genotype on nasal IgE (U/mL) and histamine (nmol/L) when exposed to allergen plus clean air or allergen plus diesel exhaust particles (DEP)**

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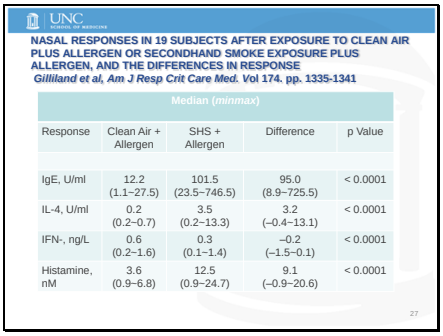

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NASAL RESPONSES IN 19 SUBJECTS AFTER EXPOSURE TO CLEAN AIR PLUS ALLERGEN OR SECONDHAND SMOKE EXPOSURE PLUS ALLERGEN, AND THE DIFFERENCES IN RESPONSE

Gilliland et al, Am J Resp Crit Care Med. Vol 174. pp. 1335-1341

	Median (*minmax*)			
Response	Clean Air + Allergen	SHS + Allergen	Difference	p Value
IgE, U/ml	12.2 (1.1–27.5)	101.5 (23.5–746.5)	95.0 (8.9–725.5)	< 0.0001
IL-4, U/ml	0.2 (0.2–0.7)	3.5 (0.2–13.3)	3.2 (–0.4–13.1)	< 0.0001
IFN-, ng/L	0.6 (0.2–1.6)	0.3 (0.1–1.4)	–0.2 (–1.5–0.1)	< 0.0001
Histamine, nM	3.6 (0.9–6.8)	12.5 (0.9–24.7)	9.1 (–0.9–20.6)	< 0.0001

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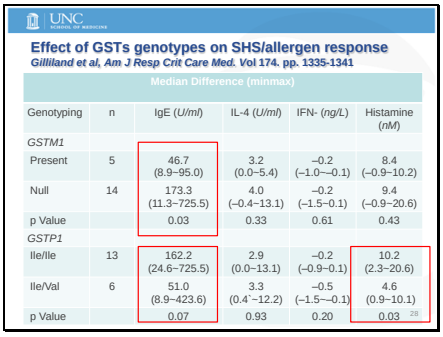

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Effect of GSTs genotypes on SHS/allergen response

Gilliland et al, Am J Resp Crit Care Med. Vol 174. pp. 1335-1341

		Median Difference (minmax)			
Genotyping	n	IgE (*U/ml*)	IL-4 (*U/ml*)	IFN- (*ng/L*)	Histamine (*nM*)
GSTM1					
Present	5	46.7 (8.9–95.0)	3.2 (0.0–5.4)	–0.2 (–1.0—0.1)	8.4 (–0.9–10.2)
Null	14	173.3 (11.3–725.5)	4.0 (–0.4–13.1)	–0.2 (–1.5–0.1)	9.4 (–0.9–20.6)
p Value		0.03	0.33	0.61	0.43
GSTP1					
Ile/Ile	13	162.2 (24.6–725.5)	2.9 (0.0–13.1)	–0.2 (–0.9–0.1)	10.2 (2.3–20.6)
Ile/Val	6	51.0 (8.9–423.6)	3.3 (0.4`–12.2)	–0.5 (–1.5—0.1)	4.6 (0.9–10.1)
p Value		0.07	0.93	0.20	0.03

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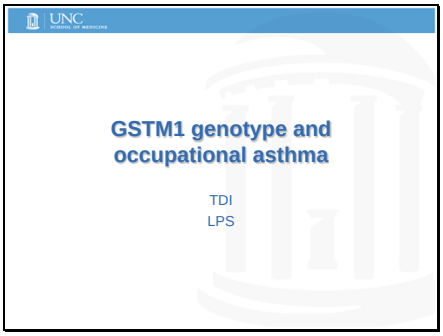

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GSTM1 genotype and occupational asthma

TDI

LPS

Slide 30

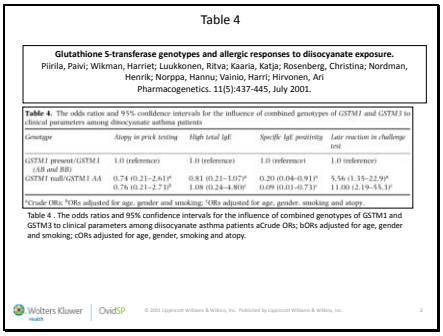

Table 4

Glutathione S-transferase genotypes and allergic responses to diisocyanate exposure.

Pirila, Paivi; Wikman, Harriet; Luukkonen, Ritva; Kaaria, Katja; Rosenberg, Christina; Nordman, Henrik; Norppa, Hannu; Vainio, Harri; Hirvonen, Ari

Pharmacogenetics. 11(5):437-445, July 2001.

Table 4. The odds ratios and 95% confidence intervals for the influence of combined genotypes of *GSTM1* and *GSTM3* to clinical parameters among diisocyanate asthma patients

Genotype	*Atopy in prick testing*	*High total IgE*	*Specific IgE positivity*	*Late reaction in challenge test*
GSTM1 present/*GSTM3* (*AB* and *BB*)	1.0 (reference)	1.0 (reference)	1.0 (reference)	1.0 (reference)
GSTM1 null/*GSTM3 AA*	0.74 (0.21–2.61)[a] 0.76 (0.21–2.71)[b]	0.81 (0.21–3.07)[a] 1.08 (0.24–4.80)[c]	0.20 (0.04–0.91)[a] 0.09 (0.01–0.73)[c]	5.56 (1.35–22.9)[a] 11.00 (2.19–55.1)[c]

[a]Crude ORs; [b]ORs adjusted for age, gender and smoking; [c]ORs adjusted for age, gender, smoking and atopy.

Table 4 . The odds ratios and 95% confidence intervals for the influence of combined genotypes of GSTM1 and GSTM3 to clinical parameters among diisocyanate asthma patients aCrude ORs; bORs adjusted for age, gender and smoking; cORs adjusted for age, gender, smoking and atopy.

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Table 3

N-Acetyltransferase genotypes as modifiers of diisocyanate exposure-associated asthma risk.
Wikman, Harriet; Piirila, Paivi; Rosenberg, Christina; Luukkonen, Ritva; Kaaria, Katja; Nordman, Henrik; Norppa, Hannu; Vainio, Harri; Hirvonen, Ari Pharmacogenetics. 12(3):227-233, April 2002.

Table 3 Number of cases/controls and asthma risks associated with *GST* and *NAT* high-risk genotype combinations

Genotype			MDI		HDI, MDI, TDI	
			Case/control	OR* (95% CI)	Case/control	OR* (95% CI)
GSTM1	*NAT1*[a]					
Present	Fast		6/19	1.0	13/25	1.0
Null	Slow		15/18	2.34 (0.84–6.30)[c] 7.58 (1.42–40.3)[f]	43/20	4.14 (1.76–9.72)[c] 4.53 (1.76–11.6)[f]
GSTM1	*NAT2*[a]					
Present	Fast		9/14	1.0	23/19	1.0
Null	Slow		14/18	2.72 (0.82–9.10)[c] 7.34 (1.33–40.4)[f]	29/10	2.40 (0.94–6.14)[c] 3.12 (1.11–8.78)[f]
NAT1	*NAT2*[a]					
Fast	Fast		5/13	1.0	12/16	1.0
Slow	Slow		17/14	3.16 (0.90–11.0)[c] 8.02 (1.42–45.3)[f]	39/19	3.08 (1.24–7.66)[c] 4.20 (1.51–11.6)[f]

CI, confidence interval; HDI, hexamethylene diisocyanate; MDI, diphenylmethane diisocyanate; OR, odds ratio; TDI, toluene diisocyanate.
*Only statistically significant associations are shown; [b] P for interaction 0.040; [c] crude OR; [d] OR adjusted for age, gender, smoking and atopy; [e] P for interaction 0.250; [f] P for interaction 0.660.

Table 3 . Number of cases/controls and asthma risks associated withGSTandNATHigh-risk genotype combinations CI, confidence interval; HDI, hexamethylene diisocyanate; MDI, diphenylmethane diisocyanate; OR, odds ratio; TDI, toluene diisocyanate aOnly statistically significant associations are shown; bP for interaction 0.040; ccrude OR; dOR adjusted for age, gender, smoking and atopy; eP for interaction 0.250; fP for interaction 0.660.

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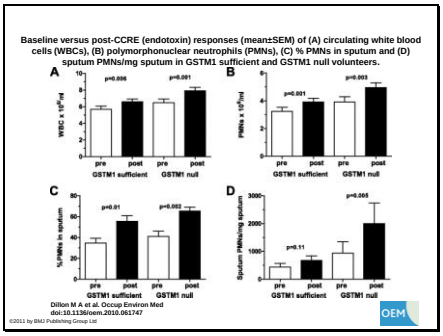

Baseline versus post-CCRE (endotoxin) responses (mean±SEM) of (A) circulating white blood cells (WBCs), (B) polymorphonuclear neutrophils (PMNs), (C) % PMNs in sputum and (D) sputum PMNs/mg sputum in GSTM1 sufficient and GSTM1 null volunteers.

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