Autism, our Personal Environments, and Toxicant-Induced Loss of Tolerance (TILT)

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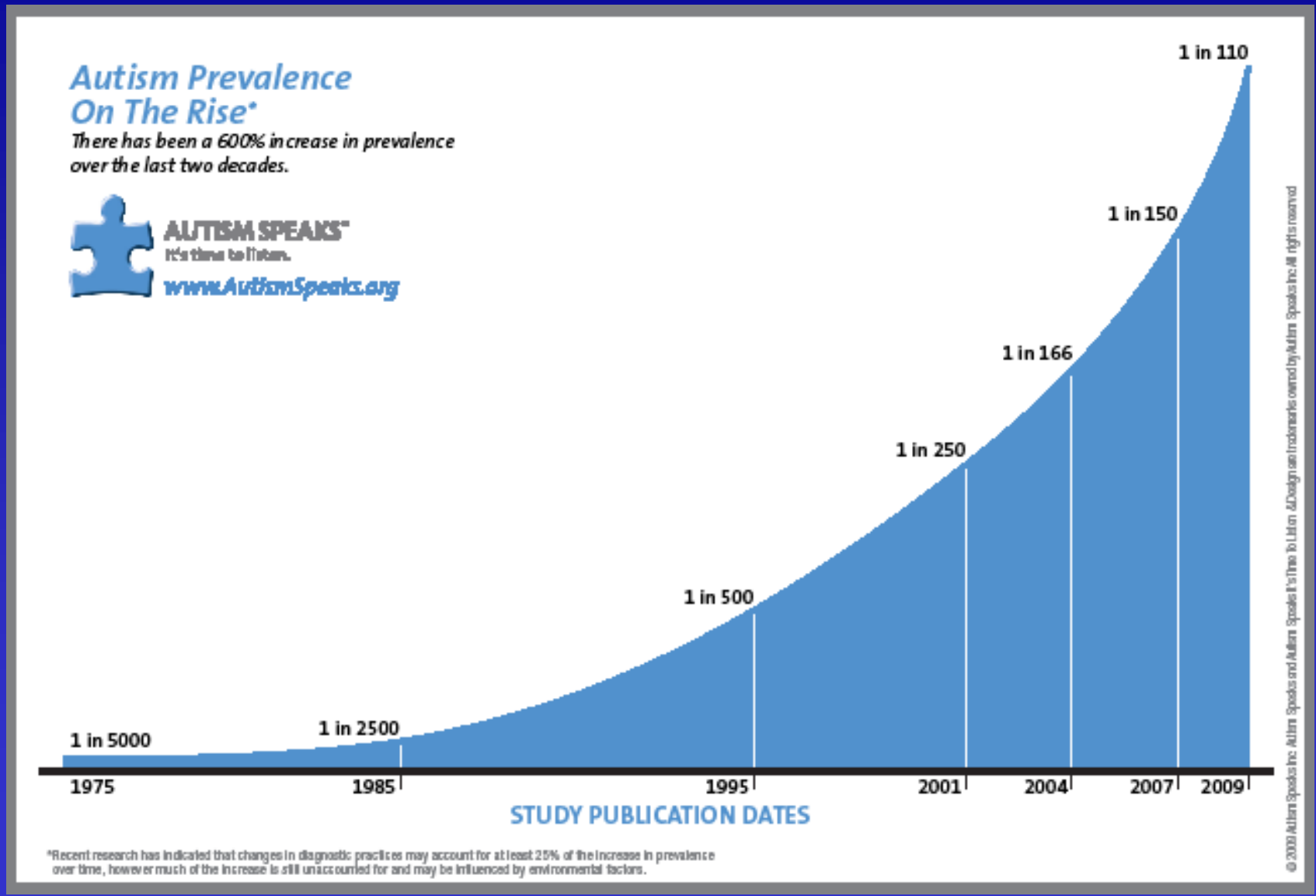
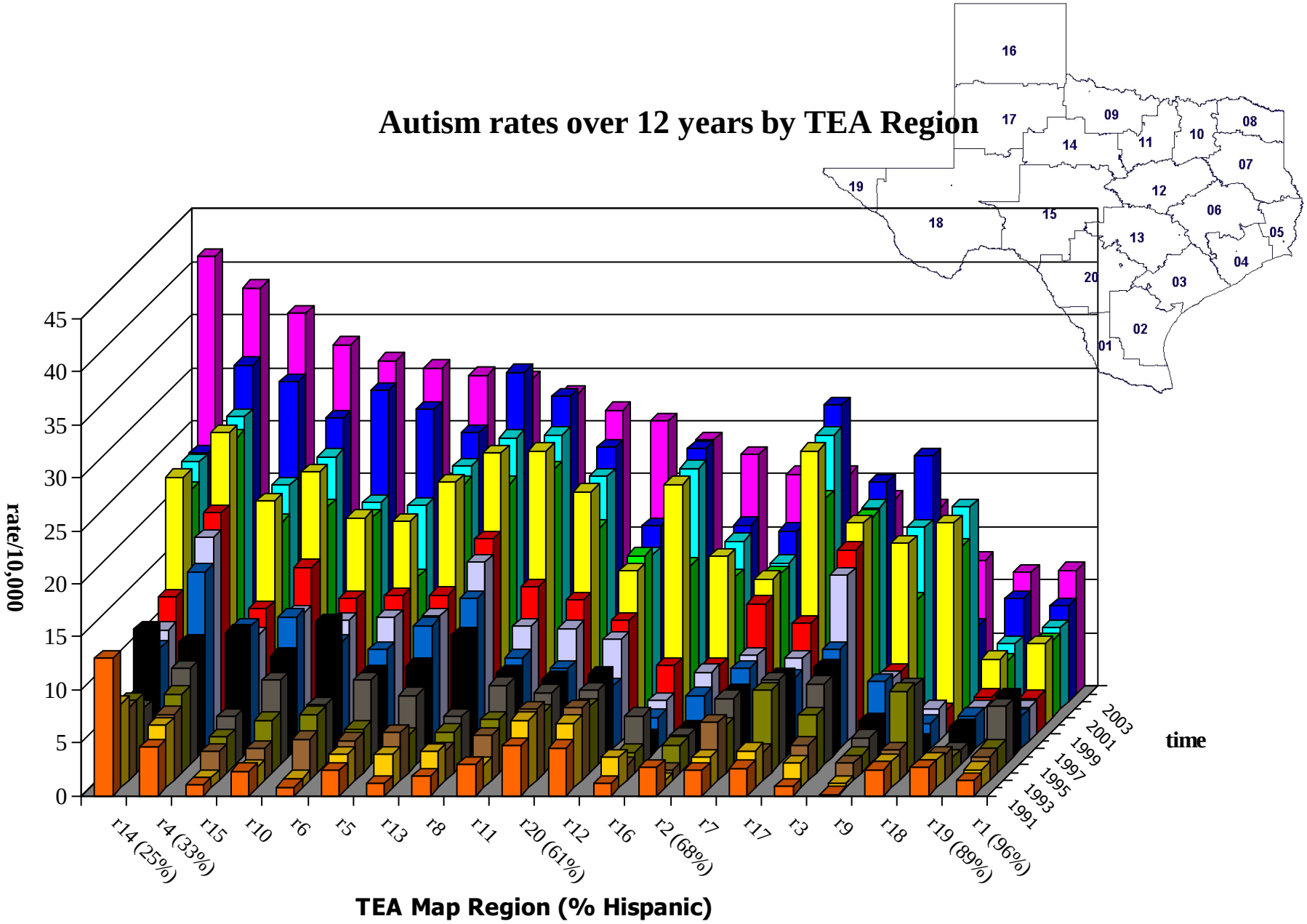
Autism Prevalence



Autism rates over 12 years by TEA Region

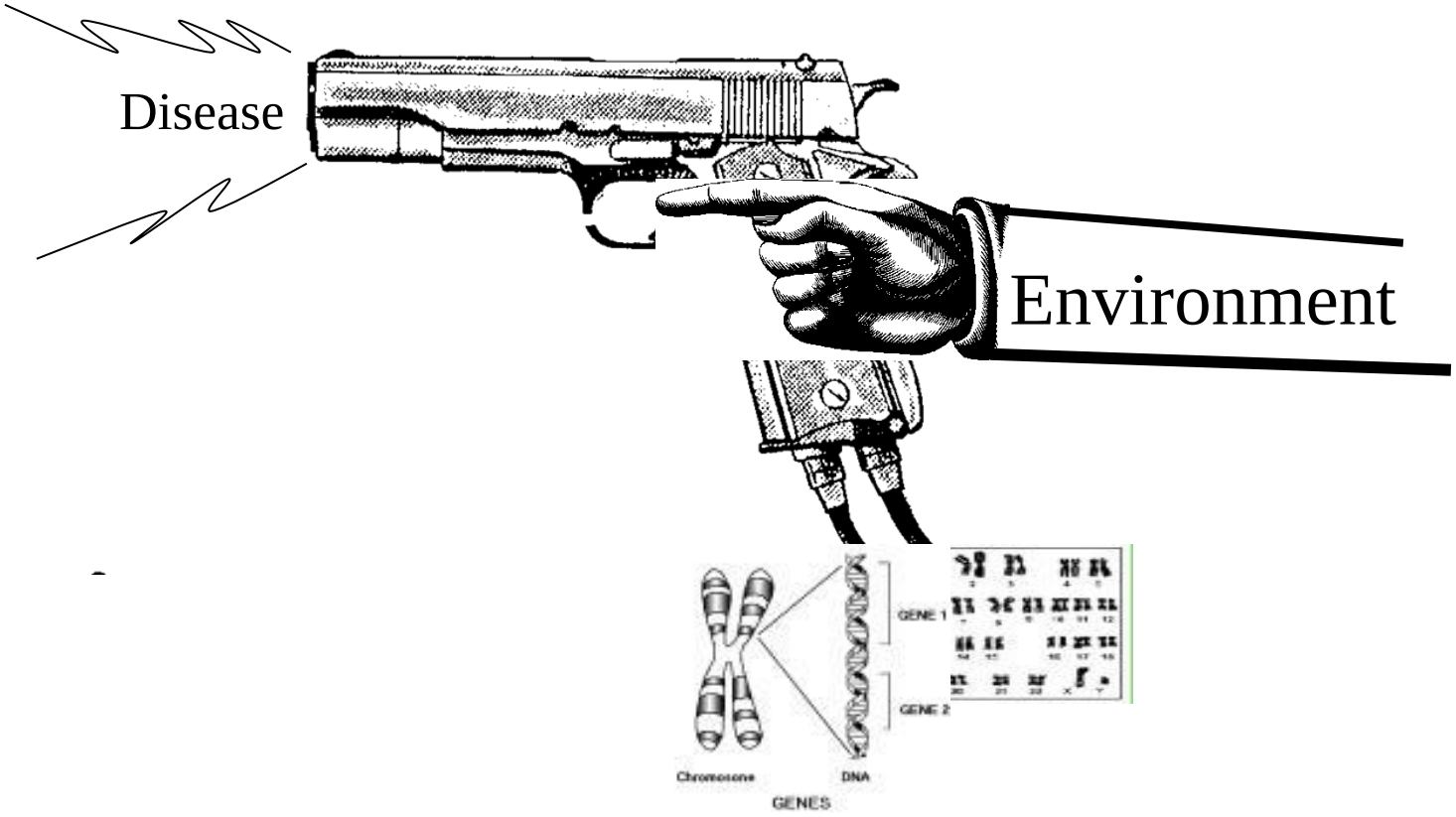


Gene-environment interactions

- There are no genetic epidemics.
- Genetics loads the gun; the environment pulls the trigger.

“Genetics loads the gun...

…but Environment pulls the trigger”



Autism Spectrum Disorders

"If you've seen one child with autism… you've seen one child with autism."

Genetic Heritability and Shared Environmental Factors Among Twin Pairs With Autism

Joachim Hallmayer, MD; Sue Cleveland, BS; Andrea Torres, MA; Jennifer Phillips, PhD; Brianne Cohen, BA; Tiffany Torigoe, BA; Janet Miller, PhD; Angie Fedele, BA; Jack Collins, MBA; Karen Smith, BS; Linda Lotspeich, MD; Lisa A. Croen, PhD; Sally Ozonoff, PhD; Clara Lajonchere, PhD; Judith K. Grether, PhD; Neil Risch, PhD

Context: Autism is considered the most heritable of neurodevelopmental disorders, mainly because of the large difference in concordance rates between monozygotic and dizygotic twins.

Objectiv of genetic environm

Design, at least 1 born betw California Department of Developmental Services.

Main Outcome Measures: Structured diagnostic assessments (Autism Diagnostic Interview–Revised and Autism Diagnostic Observation Schedule) were completed on 192 twin pairs. Concordance rates were calculated and parametric models were fitted for 2 definitions, 1 narrow (strict autism) and 1 broad (ASD).

Results: For strict autism, probandwise concordance for male twins was 0.58 for 40 monozygotic pairs (95% confidence interval [CI], 0.42-0.74) and 0.21 for 31 dizygotic pairs (95% CI, 0.09-0.43); for female twins, the concordance was 0.60 for 7 monozygotic pairs (95% CI, 0.28-0.90) and 0.27 for 10 dizygotic pairs (95% CI, 0.09-0.69). For ASD, the probandwise concordance for male twins was 0.77 for 15 monozygotic pairs (95% CI, 0.65-95% CI, 0.16- was 0.50 for 9 and 0.36 for 13 rge proportion d by shared environmental factors (95%, 95% CI, 9%-81% for autism and 58%; 95% CI, 30%-80% for ASD) in addition to moderate genetic heritability (37%; 95% CI, 8%-84% for autism and 38%; 95% CI, 14%-67% for ASD).

Conclusion: Susceptibility to ASD has moderate genetic heritability and a substantial shared twin environmental component.

Arch Gen Psychiatry.
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doi:10.1001/archgenpsychiatry.2011.76

NIH-sponsored twin study: environmental factors accounted for 55% of autism; genes only 37%.

What causes autism? Exploring the environmental contribution

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Current Opinion in Pediatrics 2010, 22:219–225

Purpose of review

Autism is a biologically based disorder of brain development. Genetic factors – mutations, deletions, and copy number variants – are clearly implicated in causation of autism. However, they account for only a small fraction of cases, and do not easily explain key clinical and epidemiological features. This suggests that early environmental exposures also contribute. This review explores this hypothesis.

Recent findings

Indirect evidence for an environmental contribution to autism comes from studies demonstrating the sensitivity of the developing brain to external exposures such as lead, ethyl alcohol and methyl mercury. But the most powerful proof-of-concept evidence pregnancy – on; and the ence that vaccines

m. Children today of them are fewer than 20% of xicity. I propose a targeted discovery strategy focused on suspect chemicals, which combines expanded toxicological screening, neurobiological research and prospective epidemiological studies.

The developing brain is exquisitely sensitive to certain environmental exposures and drugs. Less than 20% of high volume chemicals have been tested for neurodevelopmental toxicity.

Keywords

autism, developmental neurotoxicity, national children's study, toxicity testing, vaccines

Curr Opin Pediatr 22:219–225

1040-8703

Contributions of the environment and environmentally vulnerable physiology to autism spectrum disorders

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Current Opinion in Neurology 2010, 23:103–110

Purpose of review

This review presents a rationale and evidence for contributions of environmental influences and environmentally vulnerable physiology to autism spectrum disorders (ASDs).

Recent findings

Recent studies suggest a substantial increase in ASD prevalence above earlier Centers for Disease Control figures of one in 150, only partly explicable by data artifacts, underscoring the possibility of environmental contributors to increased prevalence. Some gene variants in ASD confer altered vulnerability to environmental stressors and exposures. De-novo mutations and advanced parental age as a risk factor for ASD also

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Summary

Prevalence, genetic, exposure, and pathophysiological evidence all suggest a role for environmental factors in the inception and lifelong modulation of ASD. This supports the need for seeking targets for early and ongoing medical prevention and treatment of ASD.

Keywords

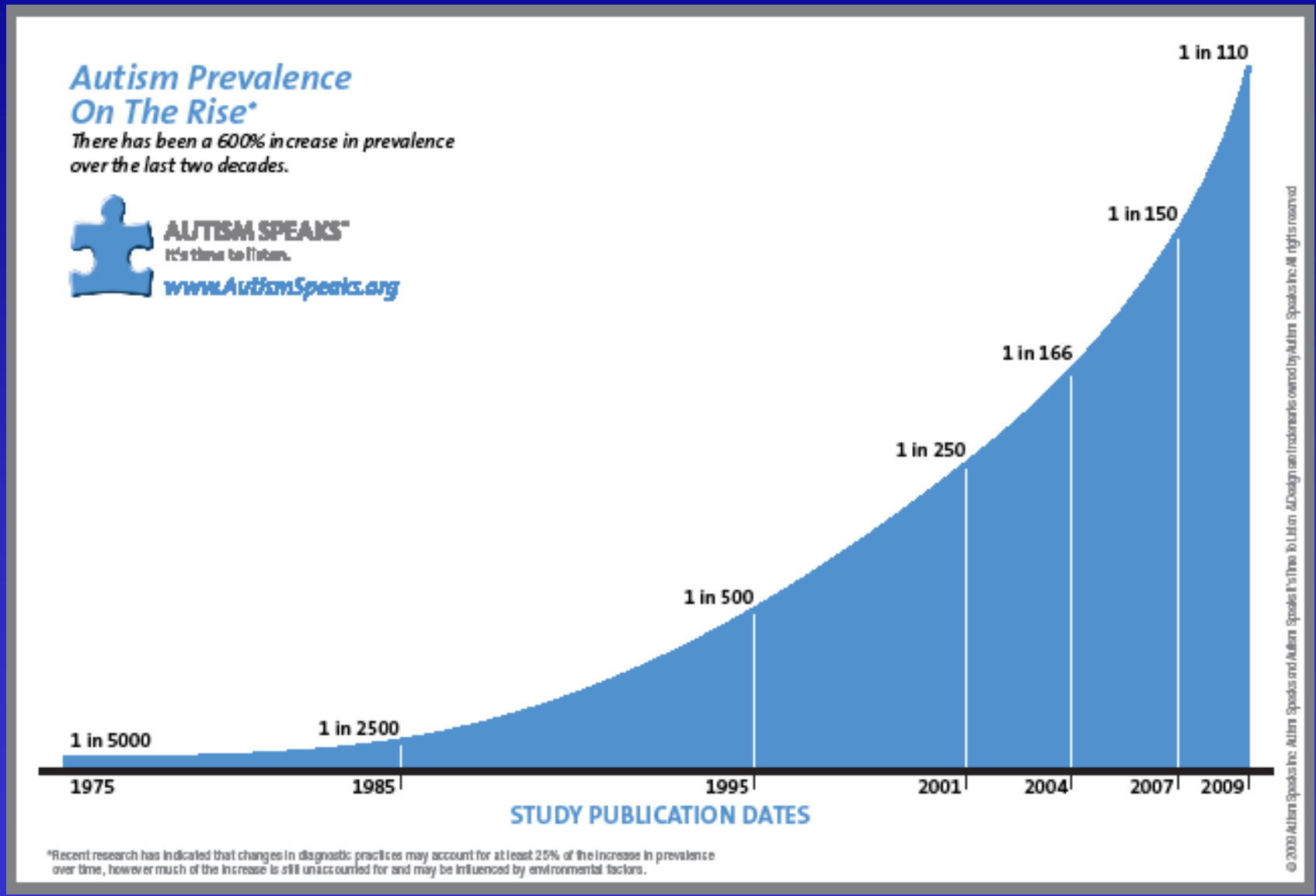
autism, dynamic encephalopathy, environment, glutathione, oxidative stress, pathophysiology

Curr Opin Neurol 23:103–110

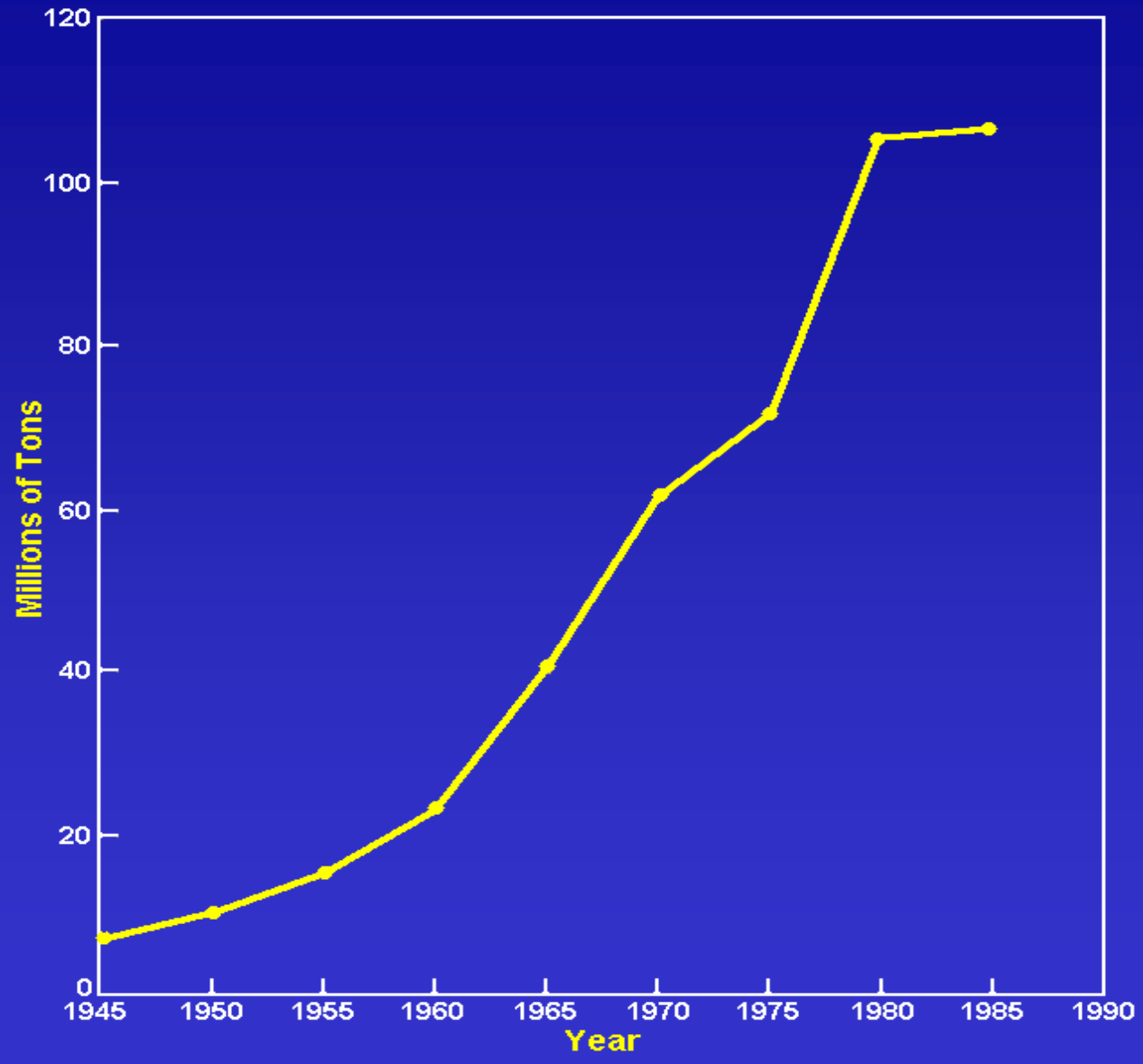
1350-7540

In some children, autism symptoms have improved and even disappeared following environmental and dietary interventions.

Autism Prevalence

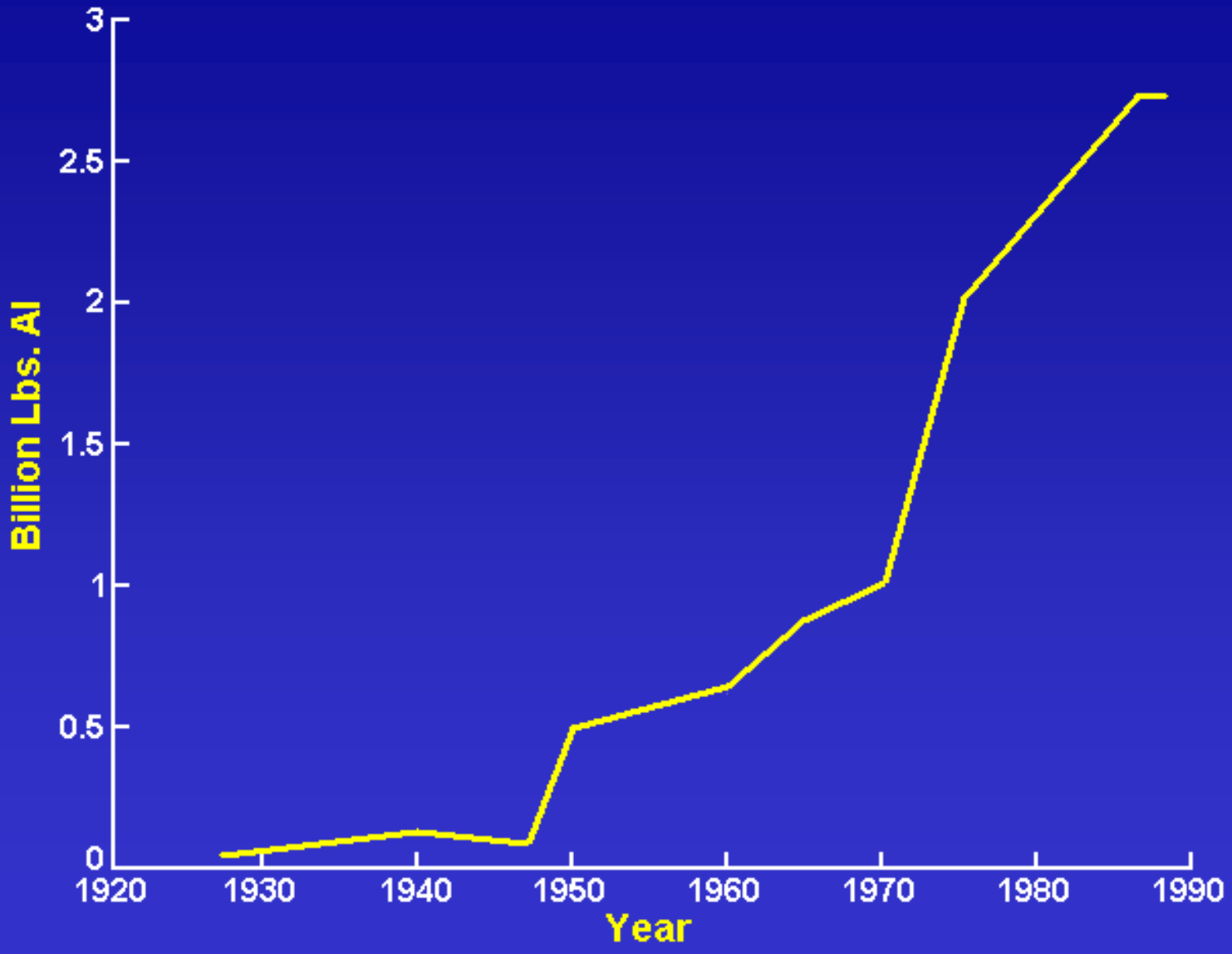


Synthetic organic chemical production
United States, 1945 - 1985



Source: U.S. Intern. Trade Commission

U.S. pesticide production, All types, 1927-1988



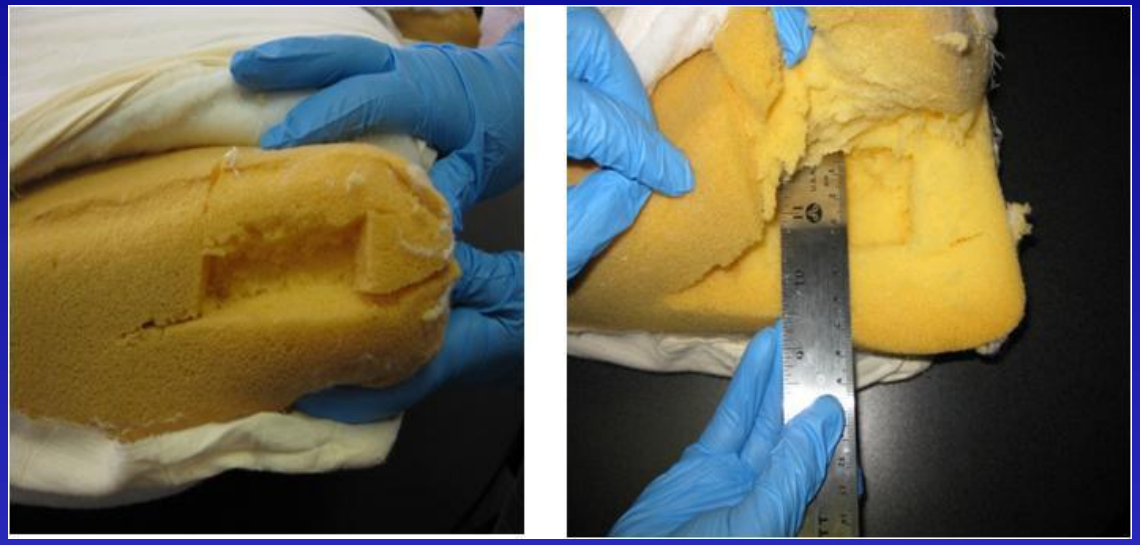
Source: EPA Market Estimates, 1986, 1988; Pimentel & Andow, 1984; Metcalf, 1980.

Indoor air is important

90% of Americans spend 90% of the day indoors (office, home, school, vehicle)

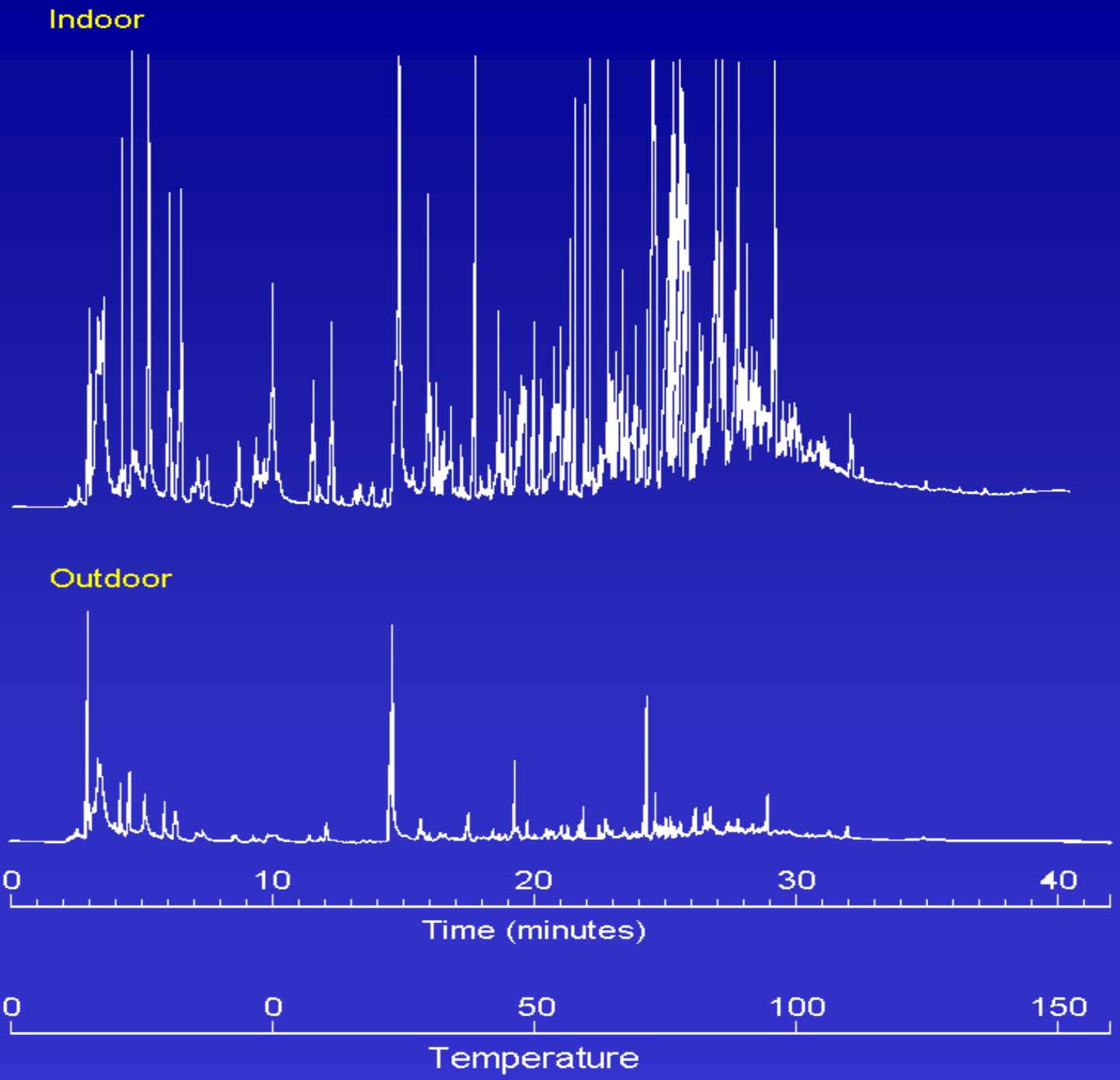
- Increased indoor air pollution sources
- Decreased fresh air intake
- Evolutionarily novel substances

Half-life for pesticides indoors

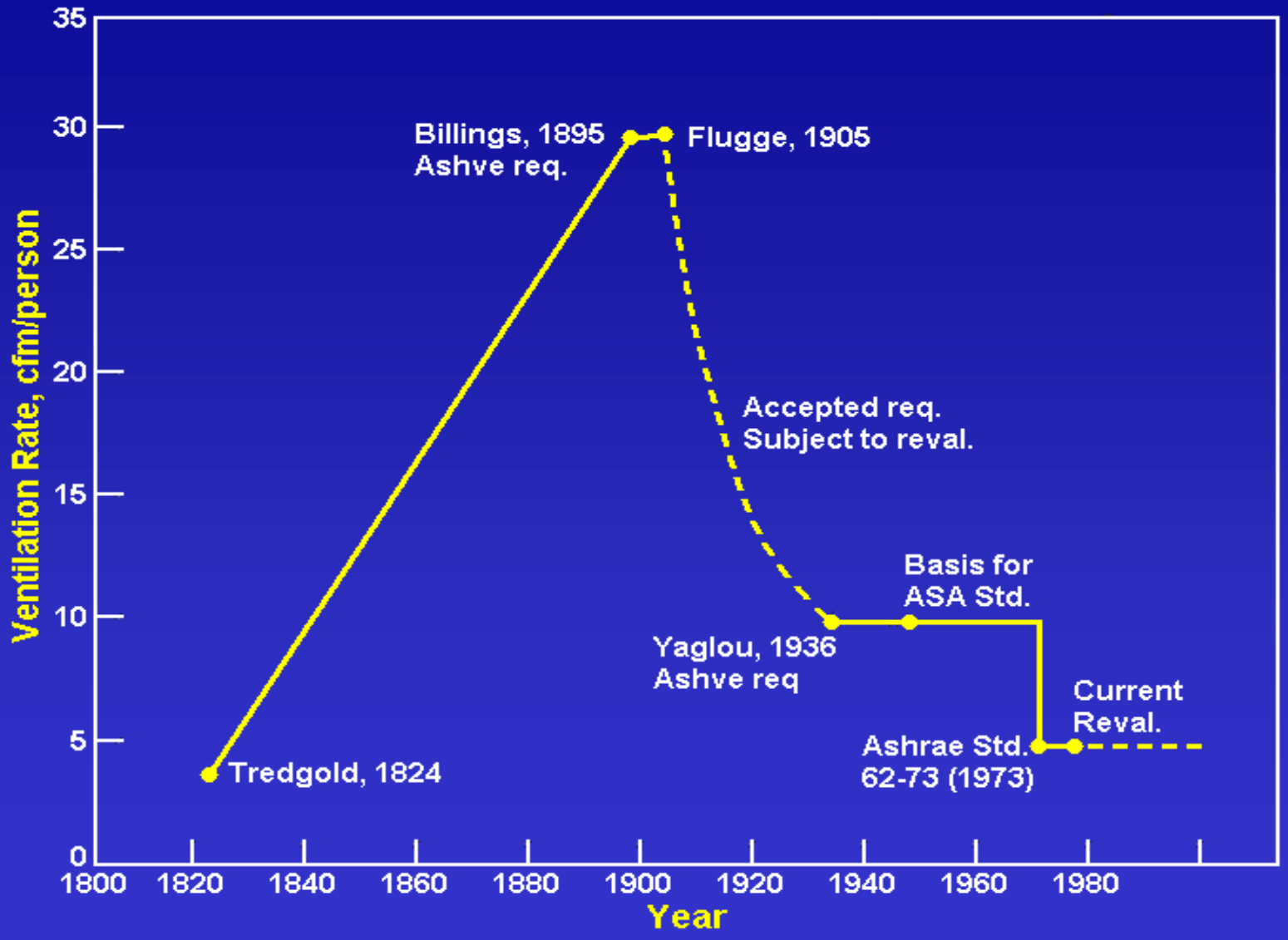


- Tested foam cushions in homes treated with pesticides
- Very long half-life
- Chlorpyrifos 4.5 – 6 years

(Camann et. al, 2011)

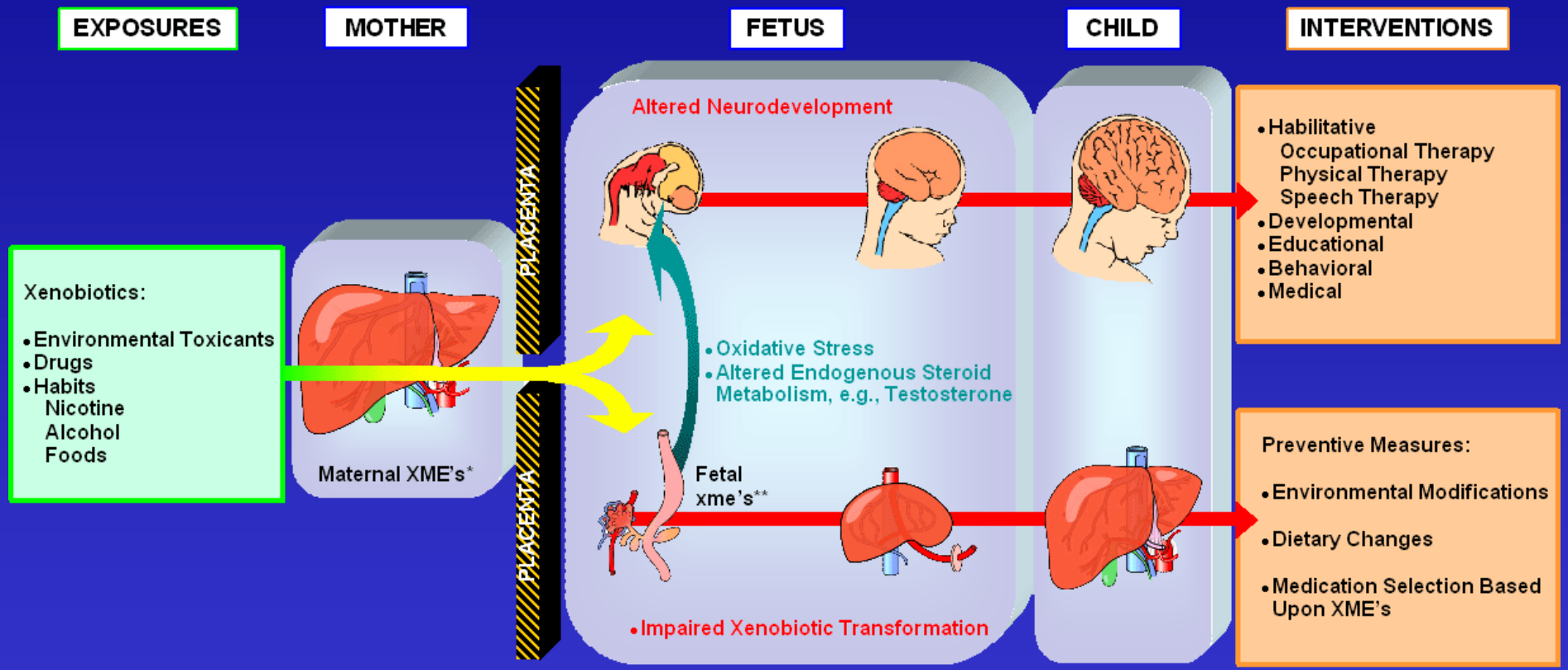

Indoor
Outdoor
0
10
20
30
40
Time (minutes)
0
0
50
100
150
Temperature

Historical development of ventilation standards in the U.S.



Mage and Gammage 1985, Evaluation of Changes in Outdoor Air Quality Occurring over the Past Several Decades, In Indoor Air and Human Health. Gammage and Kaye Eds., Chelsea, MI, Lewis Publishers, p. 13)

Impact of xenobiotic exposures on neurodevelopment



* XME's = Xenobiotic Metabolizing Enzymes in Mother
**xme's = Xenobiotic Metabolizing Enzymes in Fetus

Genetic polymorphisms linked to differences in toxicant and drug metabolism

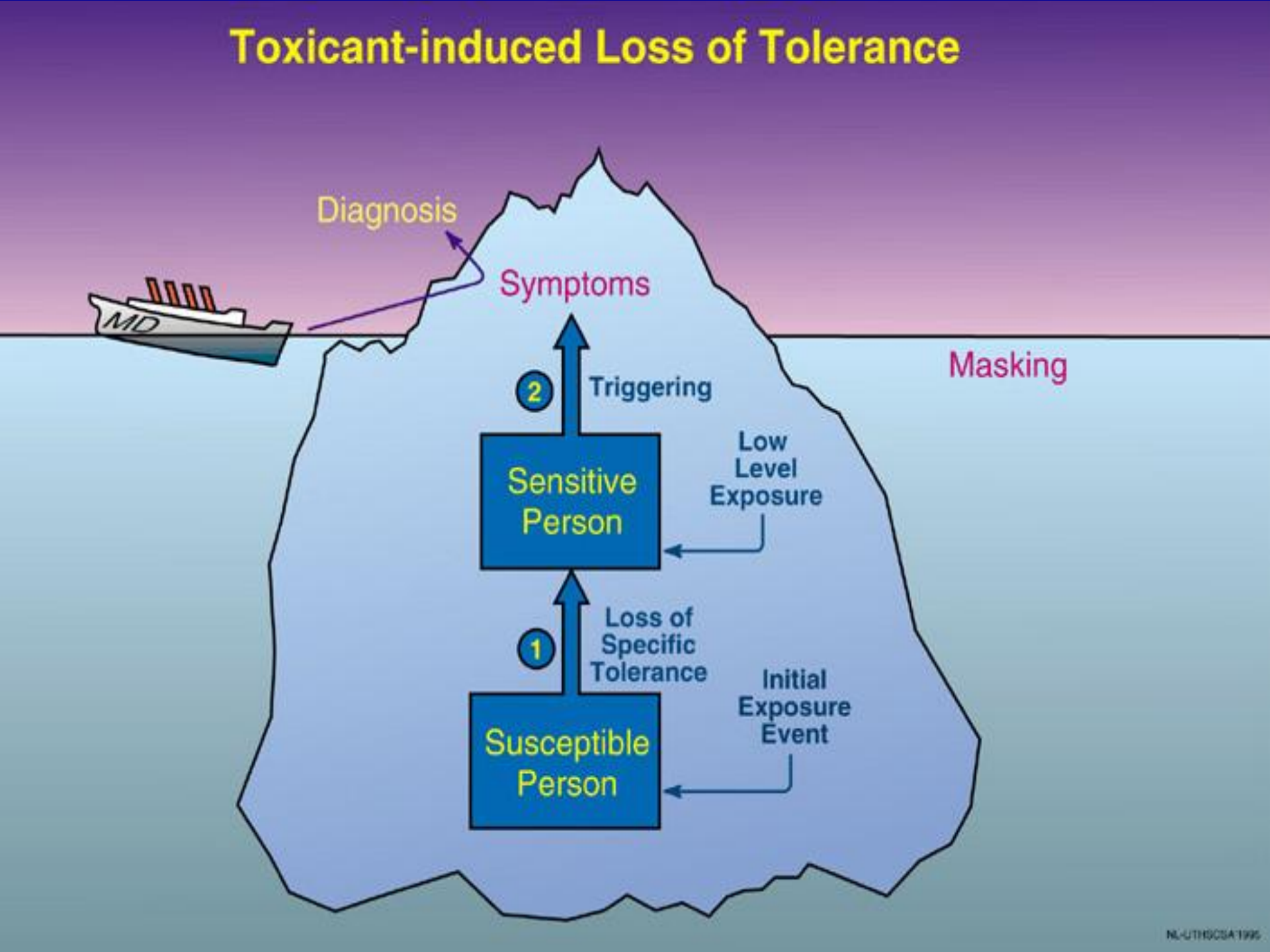
- CYP2D6
- NAT2
- PON1
- CYP2D6 + NAT2 polymorphisms together have been linked to 18x greater risk for chemical intolerance

Source: Intl J Epi 2004:33:971-978

Chemical Intolerance

- About 5-15% of people report multiple chemical intolerances
- “Do you consider yourself sensitive to everyday chemicals like those in household cleaning supplies, paints, perfumes, soaps, garden sprays, or things like that?” (15%)
- Frequently, intolerances also include foods, medications, alcoholic beverages, and caffeine.

Toxicant-induced Loss of Tolerance

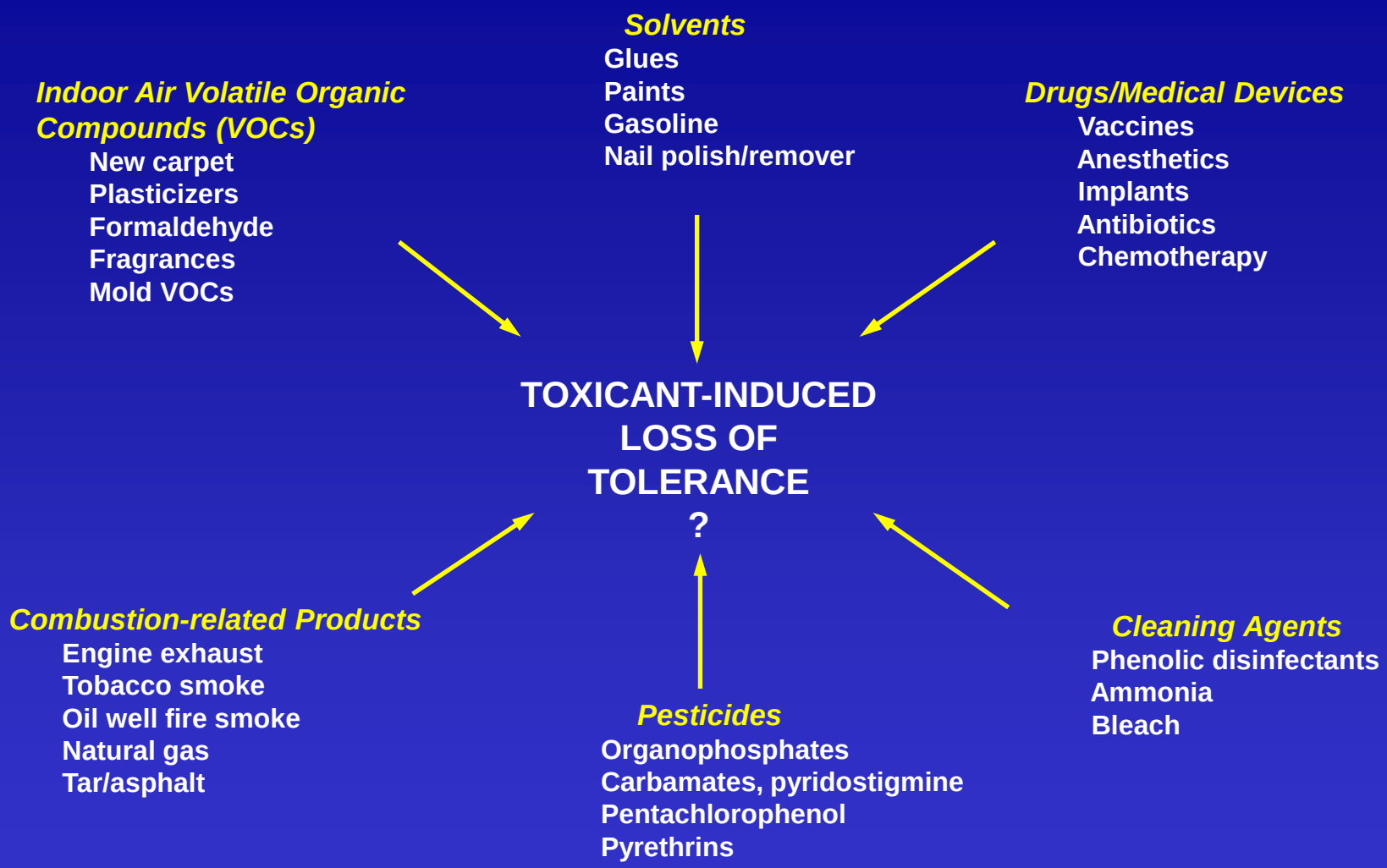


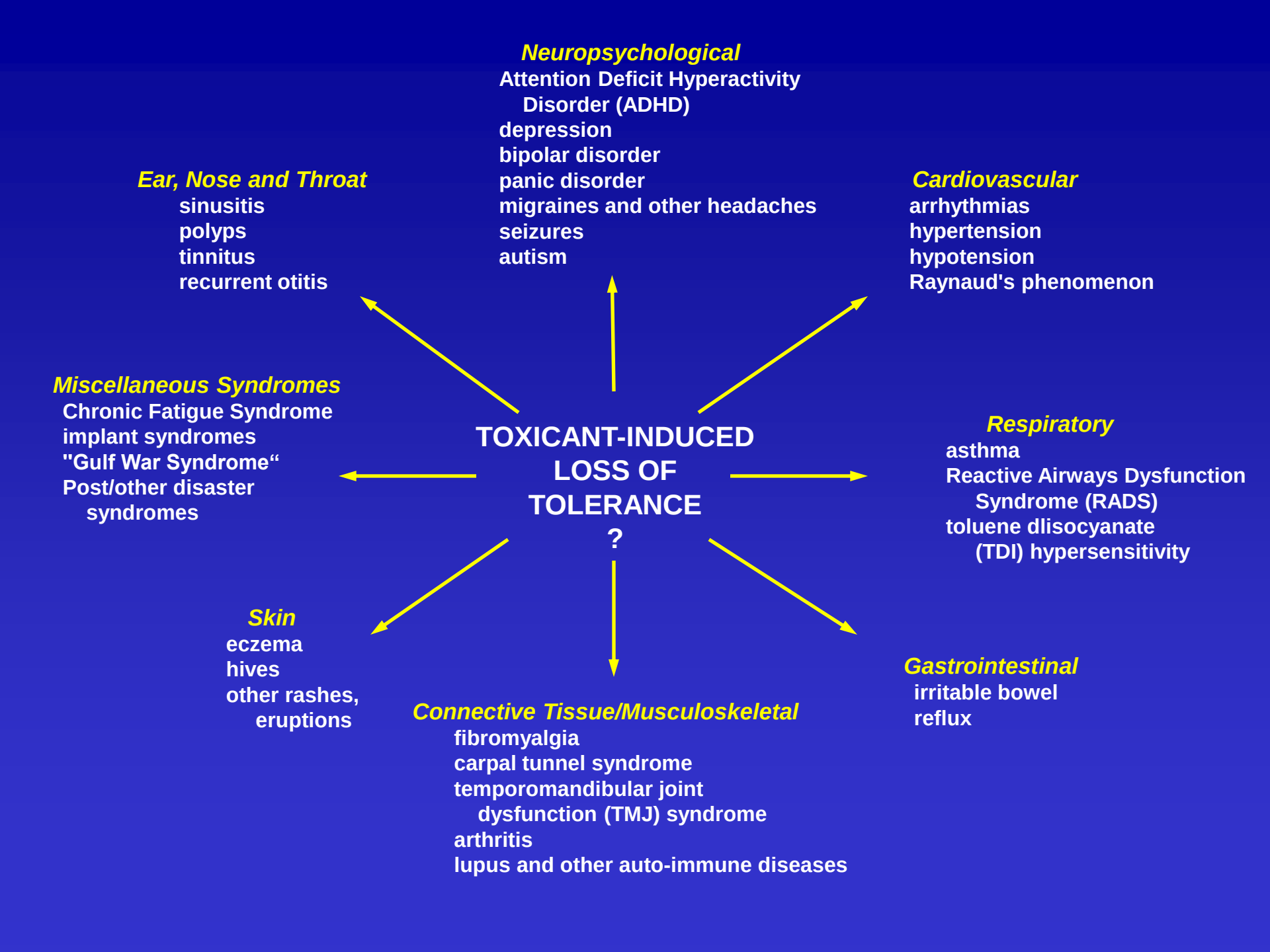
Toxicant-Induced Loss of Tolerance (TILT) involves:

- Initiating toxic exposure(s)
- Fundamental breakdown in innate tolerance
- Adverse and amplified responses to previously tolerated and structurally diverse exposures including common chemicals, foods, drugs, alcoholic beverages, caffeine

Evidence for Toxicant-Induced Loss of Tolerance

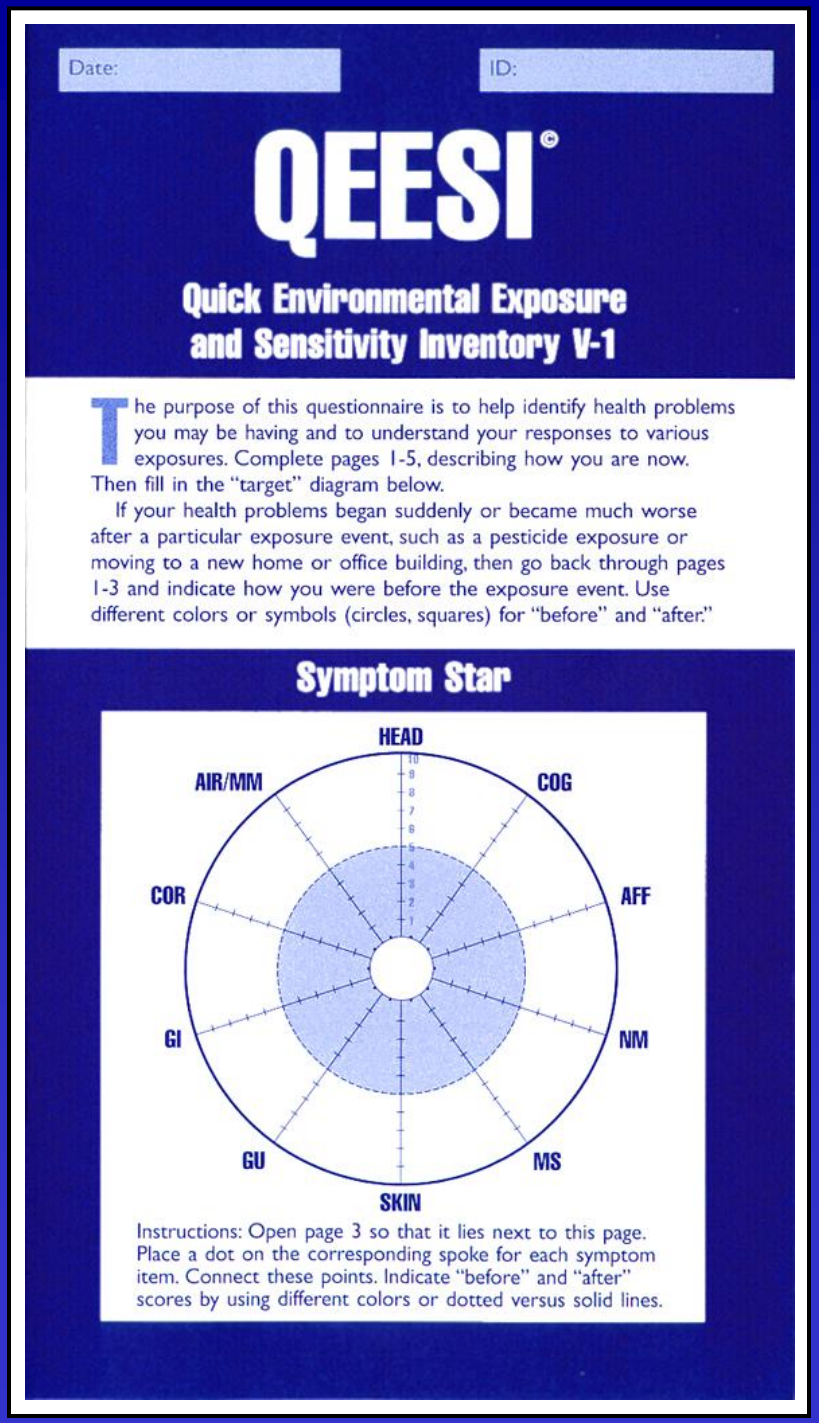
- Similar reports in different regions/countries
- Complaints of new intolerances for foods, alcoholic drinks, caffeine, and medications, *not only* chemicals = “compelling anomaly”
- Resemblance to addiction
- Plausible anatomic locus
- Recent animal models


Solvents
Glues
Paints
Gasoline
Nail polish/remover
Indoor Air Volatile Organic Compounds (VOCs)
New carpet
Plasticizers
Formaldehyde
Fragrances
Mold VOCs
Drugs/Medical Devices
Vaccines
Anesthetics
Implants
Antibiotics
Chemotherapy
TOXICANT-INDUCED LOSS OF TOLERANCE ?
Combustion-related Products
Engine exhaust
Tobacco smoke
Oil well fire smoke
Natural gas
Tar/asphalt
Pesticides
Organophosphates
Carbamates, pyridostigmine
Pentachlorophenol
Pyrethrins
Cleaning Agents
Phenolic disinfectants
Ammonia
Bleach


Neuropsychological
Attention Deficit Hyperactivity Disorder (ADHD)
depression
bipolar disorder
panic disorder
migraines and other headaches
seizures
autism
Ear, Nose and Throat
sinusitis
polyps
tinnitus
recurrent otitis
Cardiovascular
arrhythmias
hypertension
hypotension
Raynaud's phenomenon
Miscellaneous Syndromes
Chronic Fatigue Syndrome
implant syndromes
"Gulf War Syndrome“
Post/other disaster syndromes
TOXICANT-INDUCED LOSS OF TOLERANCE ?
Respiratory
asthma
Reactive Airways Dysfunction Syndrome (RADS)
toluene dlisocyanate (TDI) hypersensitivity
Skin
eczema
hives
other rashes, eruptions
Gastrointestinal
irritable bowel
reflux
Connective Tissue/Musculoskeletal
fibromyalgia
carpal tunnel syndrome
temporomandibular joint dysfunction (TMJ) syndrome
arthritis
lupus and other auto-immune diseases

The QEESI

- Validated, published questionnaire, screening tool for chemical intolerance
- 50 questions, self-administered
- 12-15 minutes to administer
- Helps people understand their symptoms and intolerances
- Differences in individual susceptibility due to:
  - Genetic predisposition, differences in detoxification ability
  - History of prior exposures



Date: ID:

QEESI®

Quick Environmental Exposure and Sensitivity Inventory V-1

The purpose of this questionnaire is to help identify health problems you may be having and to understand your responses to various exposures. Complete pages 1-5, describing how you are now. Then fill in the "target" diagram below.

If your health problems began suddenly or became much worse after a particular exposure event, such as a pesticide exposure or moving to a new home or office building, then go back through pages 1-3 and indicate how you were before the exposure event. Use different colors or symbols (circles, squares) for "before" and "after."

Symptom Star

Instructions: Open page 3 so that it lies next to this page. Place a dot on the corresponding spoke for each symptom item. Connect these points. Indicate "before" and "after" scores by using different colors or dotted versus solid lines.

Available for download at:

chemicalexposures.org

How are chemical intolerances and autism alike?

Symptoms/Intolerances	CI	Autism
Multisystem symptoms, especially neurocognitive, mood, GI	X	X
Can be initiated by pesticides and other xenobiotics	X	X
Food intolerances	X	X
Food cravings	X	X
Chemical intolerances	X	X
Drug allergies/adverse drug reactions	X	X

Mothers' report of their children's intolerances

Cases compared to controls	Odds Ratio	P-Value
Ear infections requiring tubes	**2.4**	**0.01**
Multiple infections requiring prolonged use of antibiotics	**4.5**	**0.001**
Reactions to vaccinations that prompted a call to the doctor	**3.2**	**0.02**
Sensitivity to odors such as smoke, nail polish remover, exhaust, gasoline, air fresheners, or cleaning supplies	**1.4**	**0.25**
Food allergies or intolerances	**2.8**	**0.007**
Strong food preferences/cravings	**7.0**	**0.001**
Sick from an environmental exposure	**3.0**	**0.28**
Allergies	**2.2**	**0.01**

Simple Strategy

Protect the most vulnerable individuals and you protect everyone.

- Fetus (more developmental milestones in gestation than in the rest of life)
- Children (respiratory rate, brain development continues into mid-20s, enzymatic detoxification capacity, behaviors, e.g., hand-to-mouth activity, breathing zone)
- Sensitive adults (genetics, prior exposures)

Who is susceptible?

Impossible to know for sure. Clues:

- High QEESI scores
- Family history of chemical, food and/or drug intolerance
- Family history of TILT-related conditions

But anyone may be affected by TILT with sufficient exposure!

Next steps?

Adopt a Personal Precautionary Principle

- TILT results from gene-environment interactions.
- Avoid exposures that can cause TILT.

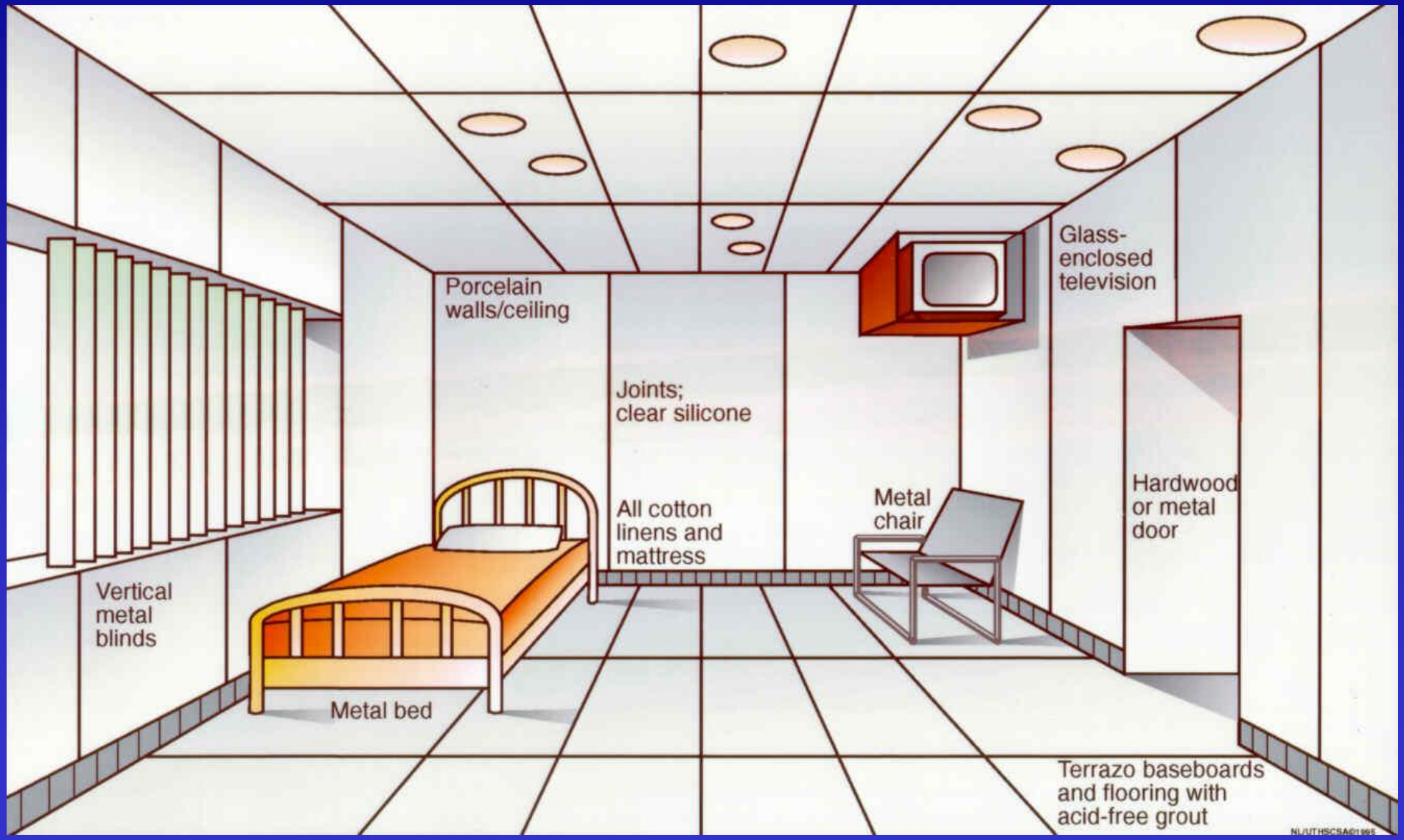
Construct Environmental Medical Units

- Research
- Diagnosis
- Treatment

Avoid exposures that can cause TILT

Instead of	Try this
Spraying pesticides	Baits, traps, and food containers
Regular paint	“No-VOC” paint
Strong cleaners	Elbow grease, soap and water, baking soda and vinegar
Scented products	Fragrance-free products
Particle board furnishings	Solid wood or metal furniture or items that have out-gassed (no odor)
New carpet	Wood or tile with washable rugs

The Environmental Medical Unit



Experimental Houses in Chemi-less Town

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The QEESI can be downloaded at no charge at:

www.chemicalexposures.org