... airborne concentrations ... which it is believed that *nearly* all workers may be repeatedly exposed ... without adverse health effects.
Health impairments considered include those that:

- shorten life expectancy,
- adversely affect reproductive function or developmental process,
- compromise organ or tissue function, or
- impair the capability for resisting toxic substances or disease processes.
HHPA Sensitization

- Hexahydrophthalic Anhydride
  - TLV®-Ceiling of 5 ug/m³ (I,V)
  - Avoid IgE and IgG mediated disease
- >50 ug/m³ yields antibody increase vs. control population
- 10 ug/m³ with peaks >50 ug/m³, increase
- 10 ug/m³ w/o peaks, no increase
- Minimizing antibody increase reduces respiratory symptoms
Ethylene metabolism yields EtO
- Hydroxyethyl hemoglobin adducts in ethylene exposed animals and humans
- DNA adducts measured in rats exposed to 300 ppm ethylene

- Saturation in rodents at 1000 ppm

- Ethylene is more than a simple asphyxiant
Ethylene metabolism

- PBPK models predict conversion rate of ethylene to EtO
  - 1000 ppm ethylene equivalent to 2-5 ppm EtO in rodents
  - 45 ppm equivalent to 1 ppm in humans
- Chronic study in rats at 3000 ppm yielded no chronic toxicologic or carcinogenic effects
- Toxic effects in humans not reported below level of asphyxiation
2004 Notice of Intended Changes for Ethylene TLV®

- TLV®-TWA of 200 ppm based on chronic study with NOAEL of 3000 ppm
- A4, Not Classifiable as a Human Carcinogen, based on negative rat bioassay
- Skin, sensitization and reproductive effects all negative
- Critical Effect: asphyxiation
Neurotoxicity Endpoints

- Toluene TLV® of 50 ppm based on reports of headache and irritation as low as 50 ppm
- Conflicting reports of altered CNS performance
- Toluene-ethanol interactions well recognized
- New literature regarding vision effects
Are vision effects real and/or relevant?


- Boyes’ Presentation on Neurotoxicity Endpoints, presented to the ACGIH® TLV®-CS Committee, Jan 2004 Meeting

  William K. Boyes
  Neurotoxicology Division
  National Health and Environmental Effects Research Laboratory
  Office of Research and Development
  U.S. Environmental Protection Agency
Boyes’ Outline

- Overview of neurotoxicity
  - Outcomes
  - Measurements
  - Risk assessment
- “Non-traditional” measures of neurotoxicity
  - Vision
    - Contrast sensitivity
    - Color
  - Hearing
    - Chemical interactions with noise-induced hearing loss
Neurotoxicity Definitions
(EPA Neurotoxicity Risk Assessment Guidelines)

- **Neurotoxicity:**
  - An adverse effect on the structure or function of the central and/or peripheral nervous system relating to exposure to a chemical substance

- **Adverse Effects:**
  - Alteration from baseline which alters the ability to survive, reproduce or adapt
  - Side effects or unwanted effects
# Neurotoxicity Outcomes

reported for >25 chemicals out of 750

*(Anger and Johnson, 1985)*

<table>
<thead>
<tr>
<th>Motor</th>
<th>Sensory</th>
<th>Cognitive</th>
<th>General</th>
<th>Affect/Personality</th>
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<tbody>
<tr>
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<td>Auditory</td>
<td>Confusion</td>
<td>Anorexia</td>
<td>Apathy</td>
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<td>Ataxia</td>
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<td>Speech</td>
<td>ChE inhibition</td>
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<tr>
<td>Incoordination</td>
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<td>Paralysis</td>
<td>Pain, feelings of</td>
<td>Fatigue</td>
<td>Hallucinations</td>
<td></td>
</tr>
<tr>
<td>Pupil size</td>
<td>Tactile</td>
<td>Narcosis</td>
<td>Irritability</td>
<td></td>
</tr>
<tr>
<td>Reflex abnormal</td>
<td>Vision</td>
<td>Neuropathy</td>
<td>Nervousness</td>
<td></td>
</tr>
<tr>
<td>Tremor</td>
<td></td>
<td></td>
<td>Restlessness</td>
<td></td>
</tr>
<tr>
<td>Weakness</td>
<td></td>
<td></td>
<td>Sleep disturbed</td>
<td></td>
</tr>
</tbody>
</table>

### Affect/Personality
- Apathy
- Delirium
- Depression
- Excitability
- Hallucinations
- Irritability
- Nervousness
- Restlessness
- Sleep disturbed
The Retina is Susceptible to Toxicity

- Retina
  - high metabolic rate
  - high choroidal blood flow
  - daily turnover of rod and cone outer segments
  - melanin
  - light-toxicant interactions

- Contrast sensitivity
- Color discrimination

http://webvision.med.utah.edu/index.html
Contrast Sensitivity

Visual Contrast
- The luminance difference between light and dark parts of a visual pattern

Contrast Sensitivity
- Expressed as the inverse of the perceptual contrast threshold
- Reflects the ability to distinguish visual features on different spatial scales

Photo by Geller
Acquired Color Vision Deficits

- Mixed organic solvents
- Styrene
- Toluene
- Perchloroethylene
- Methanol
- Ethanol

- Carbon disulfide
- n-Hexane
- Mercury
- Diethyl ether

Clinical Retinopathies
- Diabetic
- Age-related macular degeneration
- etc...
Color Confusion Index (CCI)

CCI = sum of the distances in color space between the chips as arranged / minimal distance

= 1.0 for a perfect score
Are Visual Effects Reversible?

- **Weekend**: toluene
  - color vision impaired Wed and Mon Morning
- **1 mo holiday**: styrene
  - color deficits persist
- **2 yr follow-up**: drycleaners
  - ↑ exposure → ↑ CCI,
  - ↓ exposure → CCI unchanged
- **2 yr ↓ exposure**: mixed
  - better color discrimination
  - no change in contrast sensitivity
- **2 yr post-exposure**: mixed
  - color vision not impaired
  - contrast sensitivity deficits were observed
Boyes’ Summary: Visual Effects

- Organic solvents
  - cause deficits in visual contrast sensitivity contrast
  - cause deficits in color perception
- The effects
  - may be subtle in magnitude
  - but increase with continued exposure
- The locus of these effects
  - is unknown
  - may involve photoreceptors or other retinal neurons
- Recovery
  - is uncertain
- Dose levels
  - are among the lowest reported to cause adverse effects
Hydrocarbon Mixtures

• Chemist’s point of view:
  • aliphatic, cycloaliphatic & aromatic alkanes, alkenes & alkynes, ketones, aldehydes, alcohols, ethers, etc.

• Solvent User’s point of view:
  • Fuels, synthesis feedstocks, cleaning solvents, coating & adhesive vehicles, etc.
TLV® Values

- Pure substances: several hundred
- Substance Mixtures: ten
  - Asphalt, Coal tar pitch volatiles, Diesel fuel, gasoline, kerosene/jet fuels, LPG, Rubber solvent (naphtha), Stoddard solvent, Turpentine, VM&P Naphtha
Hc Mixture Emphasis

- Recent Adoptions
  - Kerosene/Jet Fuels, as total hydrocarbon vapor
  - Turpentine and selected monoterpenes
  - Aliphatic hydrocarbon gases Alkane (C$_1$-C$_4$)
  - Diesel Fuel
Substance Group Approach to Hydrocarbon Mixtures

• $C_1$-$C_4$ Aliphatic Alkane gases was successful
• RCP -- European and American chemical industry “Hydrocarbon Panels” have jointly developed a method to develop OELs for hydrocarbon solvents.
• Two necessary parts:
  • Calculation procedure
  • “Guidance Values” for hydrocarbon groups
Calculation Procedure for Mixtures

Objective:
To develop a generic method for setting exposure limits for hydrocarbon solvents.

Generic:
• Include all hydrocarbon solvents
• Maximum advantage of existing data
• Minimize effects of minor differences
• Similar solvents have similar TLVs®
Hc Mixture Challenges

- Huge amount of information available
- Large body of un-published data
- User perspective
  - Manufacturer recommended OEV
  - IH comparison with measured results
- Liquid vs. Vapor % issues
- Overlap of “blends”