Chronic Exposure to Neurotoxic Factors and Sense

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Outline
• Chronic exposure ?
• Neurotoxic substances ?
• What do we have ? How do we gather data for information? And what is its use?
• Exposure and Effect relationship-- Chronic exposure
• Senses?
• (Chronic) exposure evaluation for sensory system
• Any neglect in occupational health practice-evaluation-situation?: Importance-possibilities-resources-records-reports?
• What do we need?

Chronic exposure definition?

a. Long term exposure, usually lasting one year to a lifetime. [CARB, 2000: Glossary of Air Pollution Terms];
b. Multiple exposures occurring over an extended period of time, or a significant fraction of the animal’s or the individual’s lifetime. [IRIS, 1999: Glossary of IRIS Terms];
c. A long term exposure to a chemical for a period of one year or more in animals and more than seven years in humans. [OFA, 2000: Oxyfuels Glossary];
d. A persistent, recurring, or long term exposure, as distinguished from acute. Chronic exposure may result in health effects (such as cancer) that are delayed in onset, occurring long after exposure has ceased. [REAP, 1995: Residential Exposure Assessment Project];
e. Multiple exposures occurring over an extended period of time, or a significant fraction of the animal’s or the individual’s lifetime. [USDOE, 2000: RAIS Glossary];
f. Long-term exposure usually lasting 6 months to a lifetime. [USEPA, 1995: Benchmark Dose];
g. Multiple exposures occurring over an extended period of time or over a significant fraction of an animal’s or human’s lifetime (Usually seven years to a lifetime.) [USEPA, 1997a: EPA Terms of Environment];
h. Exposure to the poison occurs over a period of weeks, months, or years; onset of signs may be sudden and dramatic, or can be insidious like a slow loss in body condition or reduced productivity. [WSU, 1999: Definitions and Abbreviations of Veterinary Terms]

ATSDR
Acute = 1 to 14 days,
Intermediate = 15 to 364 days, and
Chronic = 1 year or longer
Neurotoxic Substances

- Bis(chloromethyl) Ether
- Bromoform & Dipbromochloromethane
- Bromomethane
- Cadmium
- Carbon Disulfide
- Carbon Monoxide
- Carbon Tetrachloride
- Chlorane
- Chlordecone
- Chlorfenvimphos
- Chlorine Dioxide & Chlorite
- Chlorobenzene
- Chloroform
- Chloromethane
- Chlorpyrifos
- Cresols
- Cyanide
- DDT, DDE, DDD
- Diazinon
- Dichlorvos
- Dinitroresols
- Disulfoton
- Endosulfan
- Endrin/Endrin aldehyde
- Ethion
- Ethylbenzene
- Ethylene Oxide
- Fuel Oils / Kerosene
- Gasoline, Automotive
- Heptachlor
- Heptachlor Epoxide
- Hexachlorocyclohexane (HCH)
- Hexachloroethane
- HMX (Octogen)
- Hydraulic Fluids
- Hydrogen Sulfide
- Ionizing Radiation
- Jet Fuels JP-4 and JP-7
- Jet Fuels JP-5 and JP-8
- Lead
- Malathion
- Manganese
- Mercury
- Metallic Mercury
- Methoxychlor
- Methyl Mercaptan
- Methyl Parathion
- Methylene Chloride
- Naphthalene, 1-Methylnapthalene, 2-Methylnaphthalene
- Nutella
- Ottol Fuel II and Its Components
- Polychlorinated Biphenyls (PCBs)
- Pyrethrin and Pyrethroids
- Pyridine
- RDX (Cyclonite)
- Stoddard Solvent
- Styrene
- Tetrachloroethylene (PERC)
- Tetryl
- Thallium
- Tin and Compounds
- Toluene
- Trichloroethylene (TCE)
- Used Mineral-based Crankcase Oil
- Xylenes

Otto Fuel II and Its Components
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Used Mineral-based Crankcase Oil
Xylenes

ILO
WHO
IPCS
inchem.org
WHMIS
NIOSH, ATSDR
... ...
CAS number- MSDS

Styrene

Table 2.1: Results of Selected Human Neurotoxicity Studies

<table>
<thead>
<tr>
<th>Source</th>
<th>Reference</th>
<th>NIOSH ppm</th>
<th>LOEL ppm</th>
</tr>
</thead>
<tbody>
<tr>
<td>1994</td>
<td>Xi et al.</td>
<td>8</td>
<td>40</td>
</tr>
<tr>
<td>1994</td>
<td>Klein et al.</td>
<td>6</td>
<td>20</td>
</tr>
<tr>
<td>2002</td>
<td>Chen et al.</td>
<td>20</td>
<td>40</td>
</tr>
<tr>
<td>2002</td>
<td>Yang et al.</td>
<td>40</td>
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</tr>
<tr>
<td>2002</td>
<td>Lin et al.</td>
<td>80</td>
<td>160</td>
</tr>
<tr>
<td>2004</td>
<td>Li et al.</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>2005</td>
<td>Zhao et al.</td>
<td>30</td>
<td>60</td>
</tr>
<tr>
<td>2005</td>
<td>Wang et al.</td>
<td>60</td>
<td>120</td>
</tr>
<tr>
<td>2005</td>
<td>Sun et al.</td>
<td>120</td>
<td>240</td>
</tr>
<tr>
<td>2005</td>
<td>Wu et al.</td>
<td>240</td>
<td>480</td>
</tr>
</tbody>
</table>

Styrene is widely used to make plastics and rubber. Consumer products containing styrene include:
- Packaging materials
- Insulation for electrical uses (i.e., wiring and appliances)
- Insulation for shoes, boots, and other clothing
- Fiberglass, plastics, automobile parts
- Drinking cups and other "food-use" items
- Carpet backing

These products may contain significant levels of styrene. However, most of these products also contain a small amount of styrene.
### ATSDR Minimal Risk Levels (MRLs) - February 2012

<table>
<thead>
<tr>
<th>Route</th>
<th>Duration</th>
<th>MRL</th>
<th>Factors</th>
<th>Endpoint</th>
<th>Draft/ Final</th>
<th>CAS Number</th>
</tr>
</thead>
<tbody>
<tr>
<td>STYRENE</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Inh. Chr.</td>
<td>0.2 ppm</td>
<td>30</td>
<td></td>
<td>Neur.</td>
<td>Final 11/2010</td>
<td>100-42-5</td>
</tr>
<tr>
<td>Oral Acute</td>
<td>0.1 mg/kg/day</td>
<td>1000</td>
<td></td>
<td>Neur.</td>
<td>Final 11/2010</td>
<td>100-42-5</td>
</tr>
</tbody>
</table>

The conversion equation is based on 25 °C and 1 atmosphere:

\[ X \text{ ppm} = \frac{(Y \text{ mg/m}^3)(24.45)}{\text{molecular weight}} \]

or

\[ Y \text{ mg/m}^3 = \frac{(X \text{ ppm})(\text{molecular weight})}{24.45} \]

0.061 ppm

Guidelines are prepared for educating workers, increasing public awareness...
And...

• The investigation of chronic exposure is usually done by biological monitoring and usually clinically overt conditions can be detected which are mostly diseases and its important that some early signals of chronic exposure should be included in these guidelines.
In my opinion detection of Early sensory disturbances might be important in this perspective and simple tools may be integrated in these type of guidelines.
for example the wellknown Neurobehavioral Core Test Batery- WHO questionaire may be integrated in these type of guidelines.

And primary health care workers who is expected to diagnose the conditions early, timely ....
**Exposure-effect relationship**

- Acute or chronic
- Features of chemicals (type, danger, toxicologic, metabolism, excretion)
- Age, sex, weight, sensitivity, health status, drug usage, habits
- Working environment (thermal comfort, interactions of physical conditions, climate, pressure, interactions of organizational issues)
- Workplace - occupational health policy, enterprise scale, developing country, work organizational level
- Intake mechanism
  - Inhalation (nasal, mouth), oral (oropharyngeal, nasal), cutaneous (touch)
  - Target organs, health effects
  - Irritation, immunologic effect, toxicologic effect - systemic, peripheral - neurotoxic, carcinogenic, reproductive, hematological, liver, kidney, cardiovascular target organs

**Senses on absorption route***

- Touch - dermal exposure
- Smell - inhalation-ingestion exposure
- Taste - inhalation and ingestion exposure
- Eye - eye exposure

Since we gather all information from the environment with our senses, some neurobehavioural disturbances might be reflections of disturbed senses. Therefore early signs of sensory impairment deserve further systematic evaluation especially for follow up.

**sensory system**

- Vision, sight - ophthalmoception
- Hearing - audioception-vestibular
- Smell - olfactoception
- Taste - gustaception
- Touch - tactioception

Balance-Equilibrioception, acceleration, Thermoception, Kinesthetic sense - proprioception, Nociception, Other intensive senses
Dimensions?

- Molecular
- Cellular
  - Tissue
  - Neurological
    - Neurobehavioral
    - Psychosocial
- Social

Senses have neurobehavioral aspects each of which worth detailed evaluation. Sensory system begins in molecular level and it leads to series of events which influences our even social life. All aspects of this cascade have the potential to affect each other.

What do we have?

Questionnaires
- Q16 (Hogsted et al. 1986)- early disturbances for CNS
- Euroquest symptom questionnaire (Gilioli, 1993; Karlson et al., 2000; Chouaniere et al., 1997; Carter et al., 2002), 63 items: chronic effects due to exposure, irritative effects due to acute exposure, personality-related features

Test Batteries and computerized system versions
- Neurobehavioral Core Test Battery- Neurobehavioral core test battery NCBT ~ 40 minutes for screening
- SPES, NES, MANS, AENTB, PENTB, BARS, NESS-2-3, BEES- especially epidemiologic repeated applications;
- NEUTEST

Sensory Tests

- Smell- University of Pennsylvania
  Smell Identification Test (UPSIT), Connecticut Chemosensory clinical research center test (CCCRCRT), Sniffin’ sticks, Elsberg Levy’s blast injection method
- Visual Acuity- Snellen
- Visual Contrast Sensitivity, Color Vision (Lanthony D15 d)
- Color Vision (Lanthony D15 de saturated panel, Farnsworth-Munsell 100-hue, farnsworth D15, Ishiara plates, standard pseudoisochromatic plates- SPP2, HRR, Velhagen- )
- Visual field (Nagel Anomaloscope)

Areas of neurotoxicity assessed with neuropsychological testing

- Prior & Present Health
- Sensory
- Cognitive
- Affect & Mood
- Motor and Tremor
- Effort

Potential neurophysiological measures of neurotoxicity

- Electrotretinograms- Evoked responses from the retina in response to visual stimuli
- Flash visual evoked potentials (VEPs)- Cortical response to simple flashes of illumination
- Pattern visual evoked potentials (VEPs)- Cortically generated responses elicited by patterns of visual stimuli
- Brainstem auditory evoked potentials (BAEPs)- Responses recorded at or near the cortical surface reflecting volume-conducted electrical activity from brainstem generators in auditory pathway
- Middle and late potentials- Potentials occurring in auditory cortex approximately 10-30 ms after auditory stimulation
  “Far-field” somatosensory evoked potentials (SSSEPs)- Elicited by electrical stimulation of nerves, producing a large synchronous afferent volley in the CNS
  Cortical somatosensory potentials- Recorded from cerebral cortex after presentation of sensory stimuli or direct stimulation of the median nerve
  Cerebellar somatosensory potentials- Recorded from cerebellum after stimulation of peripheral nerve such as the ventral caudal tail nerve of rats
Color discrimination, arrangements

acquired colour vision losses are frequently tritan, sometimes termed “blue-yellow” loss
These tritan losses may progress to affect red-green colour vision

Iregren et al summarized tests for color vision in occupational health practice and suggested Lantony d-15 desaturated panel for its sensitivity and simplicity

Contrast sensitivity

Contrast sensitivity loss may reflect long-term cumulative chronic exposure possibly irreversible damage in neuro-optic pathway.

Inorganic mercury can reduce perception of colour and visual contrast sensitivity and peripheral visual field. Lead may impair visual contrast sensitivity-solvents, carbondi-sulfide, hegzan, perchloroethylene, styrene, toluene, solvent mixtures, pesticides chlorpyrifos color vision and visual contrast sensitivity. Trichloroethylene, ethyl benzene

Nanoparticles

1,3-Butadiene
1,4-Dioxane
2-Butanone
Acrolein
Ammonia
Carbon Disulfide
Chlorine
Chlorine Dioxide & Chlorite
Dichlorobenzenes
Ethylene Oxide
Fluorine, Hydrogen Fluoride, and Fluorides

Fuel Oils / Kerosene
Hydrogen Sulfide
Lead
Mercury
Naphthalene, 1-Methylnaphthalene, 2-Methylnaphthalen
Nitrophenols
Stoddard Solvent
Styrene
Sulfur Mustard
White Phosphorus

Vision

Molecular
Cellular
Tissue
Neurological
Neurobehavioral
Psychosocial
Social

Rods, cones, retina
photoreceptors
neurotransmitters, optic nerve,
frontooccipital,
Cornea, lens, iris, fluids,
Complex neuronal interactions

Seeing, bright, detecting colors blue-green-red.
signs, Detecting movements, shapes, visual field, night seeing
Disability, Life -------- arts-,
sciences, ambiguity...

Sight

95
874
2843
Hearing

- Molecular
  - Neurotransmitters, cilia, haircells, mechanoreceptors,
  vestibular nerve, which extends to the vestibular nuclei in the brainstem.
  temporal lobe central cortex

- Cellular
  Ear inner-middle-external

- Tissue
  Equilibrium organs connection - Fibres from the vestibular nuclei, in turn, extend to cerebellar centres controlling eye movements, and to the spinal cord

- Neurological
  Complex neuronal interactions
  Neurobehavioral
  Psychosocial
  Hearing, equilibrium, anxiety, disability
  Communicating, understanding, warning signals, employability

- Psychological
  Temporal lobe central cortex

Ototoxic substances

Workplace chemicals thought to be ototoxic either on their own or in combination with noise include:

- Solvents, mixtures such as butanol, carbon disulfide, ethyl benzene, heptane, n-hexane, styrene, toluene, trichloroethylene and xylene;
- Metals such as arsenic, lead, manganese, mercury, dimethylmercury, inorganic mercury and organic tin, cadmium, platinum;
- Pesticides such as organophosphates and parquat; and
- Asphyxiants such as acrylonitrile, carbon monoxide and hydrogen cyanide.

Hearing damage is more likely if exposure is to a combination of substances or to a combination of the substance and noise.

Smell

- Molecular
  - Olfactory neuro epithelium, mucosa, olfactory nerves, olfactory bulb, olfactory tract

- Cellular
  - Nose, mouth

- Tissue
  - Complex neuronal interactions

- Neurological
  - Neurobehavioral
  - Psychosocial
  - Social

- Psychological
  - Personality traits, odour perception, attention, affect, mood
  - Social preferences, shopping behaviour, Detecting danger, Personality trait/Mate preference

Workplace chemicals reported...
Cadmium,
Chromium,
Nickel
Organic compounds, solvents mixtures, wood dust,
acrylate, metacrylate, hydrogen sulfide

Sniff tests-Smell
University of Pennsylvania Smell Identification Test (UPSIT),
Connecticut Chemosensory clinical research center test(CCCRCT),
Sniff'ns'sticks (EU)
Elberg Levy's blast Injection method
Olfactometer
- Obtaining olfactory evoked potential (OEP) and electro-olfactograms (EOG)
- Measuring smell thresholds
- Producing expert reports (anosmia)
- Quantitative pain measurement (with CO2), testing analgesics
- Tests with MRI and MEG

Typical gases and liquid substances used in olfactometry:
- Odorants (to stimulate the olfactory nerve):
  - Phenyl ethyl alcohol (PEA) - pleasant stimulant (artificial rose)
  - Hydrogen sulphide (H2S) - unpleasant stimulant (bad eggs)
- Pain stimulants (to stimulate the trigeminal nerve):
  - Carbon dioxide - CO2

Studies have show that taste sense is in fact more complicated than mere tongue and brain interaction...

While evaluating any taste-related problems should be asked in detail ...

eg: Among patients who denied the question "Do you have difficulties in recognizing food or beverages as sweet, sour, bitter, or salty?" no taste disorder was confirmed in 94%.
In contrast, the question "Do you have a taste problem?" identified only 10% of the patients with a taste problem.

Furthermore, patients should be questioned with regard to salivation, swallowing, chewing, oral pain, previous ear infections (possibly indicated by hearing or balance problems), oral hygiene, and stomach problems.

The stimuli used in gustometry are:
- citric acid or hydrochloric acid (sour taste),
- caffeine or quinine hydrochloride (bitter taste),
- sodium chloride (salty taste),
- saccharose (sweet taste),
- monosodium glutamate (umami taste).

Tests using principle of electrical stimulation of the tongue are not suggested.
Touch

- Molecular
- Cellular
- Tissue
- Neurological
- Neurobehavioral
- Psychosocial
- Social

Merkel cells, nociceptors, immunity(Langerhans), melanocytes
Skin, hair follicles, tongue, throat, mucosa
Complex neuronal interactions
Tactition, anesthesia, paresthesia, tingling, pricking, numbness
absorption, protection, touch, discrimination...
chemical, thermal protection

There are also many chemical substances effecting touch sense and impairment is frequently subclinical

Lead
Elemental mercury
1,1,1 trichloroethane, styrene,
solvent mixtures
n-hexane, toluene,
Acrylamide,
Organophosphate and other pesticides
Ethylene oxide
Xylene

To identify effects of chemicals these examinations have been studied;

- Vibration perception threshold (VPT),
- Two point discrimination,
- Dept sense perception,
- Temperature threshold,
- Pain threshold

Data on comparability methods are limited

Exposure assessment procedure needs:
- workers’ monitoring
- working environments’ monitoring

Workers’ monitoring
Follow health status
- Symptoms, behavioral evaluations,
- Health exams,
- Biologic monitoring,
- Chemical, metabolites-- tissue, body fluids, urine, exhaled breathing air,
Working environment monitoring
Occupational Exposure Limit values ….

MAK, TLV, TWA, STEL,
MRLS(ATSDR-2012FEBRUARY)
NOAEL - no observed adverse effect level
LOAEL - lowest observed adverse effect level· ‘less serious’, ‘serious’
AOEL - acceptable operator exposure level

Is biologic and environmental monitoring possible
for chronic exposure
in «real workplaces» and «real world» of
developing countries ???

Chronic exposure is a complicated issue even for the developed countries especially when we consider the potential confounding effect of other environmental factors.

Even limit values had been detected and kept we can never be sure about the bodily responses of individuals.

NEUROTOXICITY OF CHEMICALS
EXPOSURE - EFFECT RELATIONSHIPS

ACUTE INTOXICATION → ACUTE EFFECTS
EPISODIC ??
LONG-TERM ↔ LOW DOSE ??
Reversible ? CHRONIC EFFECTS Irreversible ?

Wellbeing: Early changes: subclinical signs: symptoms: clinical illness

Developing Countries!

Well recognised - but not well-controlled neurotoxins:
Metals, Lead, mercury
Solvents,
Pesticides-Organophosphates ... others ...

“New” generation neurotoxins
e-waste
PBDE (Polybrominated diphenyl ether)
Persistent organic pollutants
Nanomaterials related.... others ...

• Occupational health services
• Poor environmental and biologic monitoring as a survey
• lack of facilities and equipment
• inadequate information systems
• Poor case detection
• Limited resources for research competing causes of ill-health
  (health services transitions, system, organizational issues)
Control hierarchy

- Identify
- Evaluate
- Control
- Eliminate
- Substitute
- Enclose/separate

Conclusion

- Considerations should be comprehensive -- sensory system impairments might be confounders for neurobehavioral methods
- Might periodic evaluation of all senses together be an early detection tool for chronic exposure ???
- Consensus on standardized questionnaires testing sensory perception in detail
  - Not time consuming, simple, but including all traditional senses,
  - Common language for evaluating senses in chronic exposure
- For widespread use and data collection, collaboration with WHO and ILO, and recommendation and training of occupational health teams are needed

Ramazzini’s primacy

"Prevention is better than cure"

For prevention we need awareness

which can only be found when it is looked for

Let’s look for early signs of sensory disturbances