Behörde für Gesundheit und Verbraucherschutz

Universitätsklinikum Hamburg-Eppendorf

zfAM Zentralinstitut für Arbeitsmedizin und Maritime Medizin

From symptoms of intoxication to identification of the noxious agents: challenges in ambient and biomonitoring analyses

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7th International Workshop How to handle imported containers safely, Berlin, 22-23 05-2014

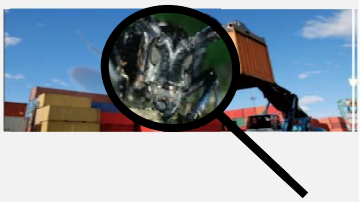
Pesticides used as fumigants are often at least as poisonous to humans as to the pests against which they are used" IMO, 2005 (International Maritime Organisation).

The fumigation of transported goods was originally introduced to protect plants and foodstuffs from infestation and destruction by pests

phytosanitary requirements

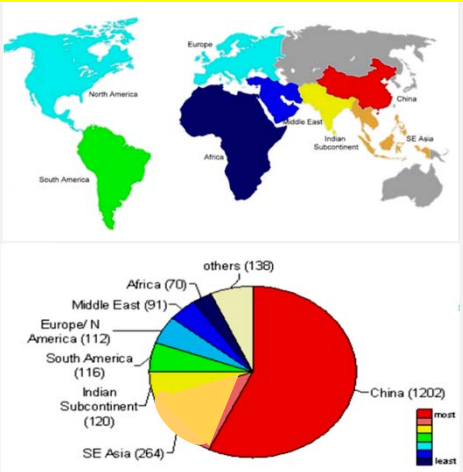
FAO (Food and Agriculture Organization) edict, ISPM No. 15, requires fumigation by methyl bromide or heat treatment of the wooden packaging and flooring material (FAO, 2007).

environmental reason (spreading alien species)



Container-Air-Measurements in Hamburg and Rotterdam
> 4000 Container air measurements (TD-GCMS-Analyses)
Studies: 2007-2013

Aim: to determine the fumigant residues in containers arriving harbor areas



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Practice:

- ✓ fumigation is becoming a standard procedure, especially in south-east Asia
- ✓ **Other fumigants than methyl bromide** (bromomethane) **are used**
- ✓ There is no labeling (< 3%)

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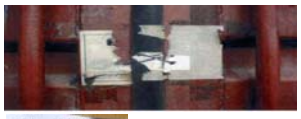
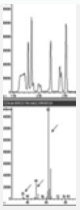


Data showed that additionally to the declared hazardous cargoes**, more than 20% of the containers were contaminated with various industrial chemicals** not declared as "dangerous".

Baur X, Poschadel B, Budnik LT. Occup Environ Med (2010)

Container-Air-Measurements in Hamburg and Rotterdam

> 4000 Container air measurements (GCMS, Flow tube mass spectrometry, TD-GCMS-Analyses) Studies: 2006-2013



1. **Study in Hamburg and Rotterdam 2006-2007 (n=2013 random samples)**
   Published in: Baur X, Poschadel B, Budnik LT. Occup Environ Med (2010)

Out of 2113 sampled import containers. **1478** were chemically contaminated **above chronic reference exposure levels** (RELs) and **761 encompass more highly contaminated containers above acute RELs**

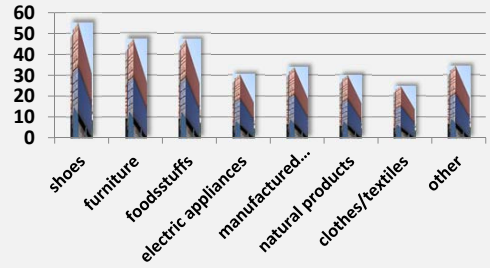
RELs (US Office of Environmental health Hazard Assessment and National Institute for Occupational Safety and Health , NIOSH) are independent science-based recomendations rather than legally applicable standards).

Container-Air-Measurements in Hamburg and Rotterdam
> 4000 Container air measurements

1. Study in Hamburg and Rotterdam 2006-2008 (2113 samples)

Published in: Baur X, Poschadel B, Budnik LT. Occup Environ Med (2010)

% fumigants above chronic RELs



REL Values in ppb (µL/m³): formaldehyde 2.44, 76; benzene 18, 410; bromomethane (methyl bromdie) 1.28, 1000; hydrogen phosphide 0.6, 300; 1,2-dichloroethane (ethylene dichloride) 98, 1000; trichloronitromethane 0.06, 100; ethylene oxide 16.6, 100; sulphuryl difluoride 5.13, 5000; hydrogen cyanide 8.2, 300.

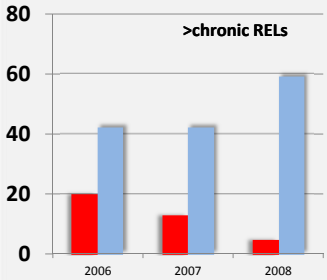
RELs (US Office of Environmental health Hazard Assessment and National Institute for Occupational Safety and Health , NIOSH) **are independent science-based recomendations for general public rather than legally applicable standards**

Container-Air-Measurements in Hamburg and Rotterdam
> 4000 Container air measurements (TD-GCMS-Analyses)

2. Study in Hamburg (additional 1201 random samples)

Published in: Budnik LT, Fahrenholtz S, Kloth S, Baur X. in J. Environ. Monit. (2010)

% of total containers



Methyl Bromide (Bromomethane), MeBr, Ethylene dichloride 1,2.dicholoethane) EDC

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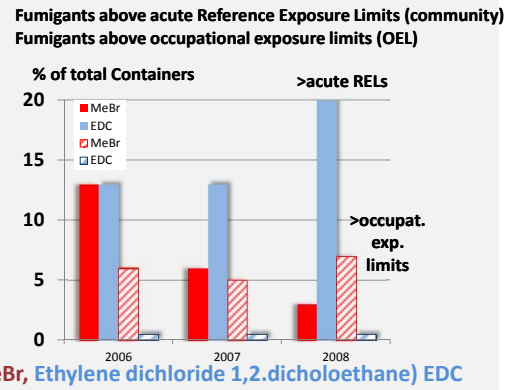


Methyl Bromide (Bromomethane), MeBr, Ethylene dichloride 1,2.dicholoethane) EDC

Container air measurements Studies: 2007-2013

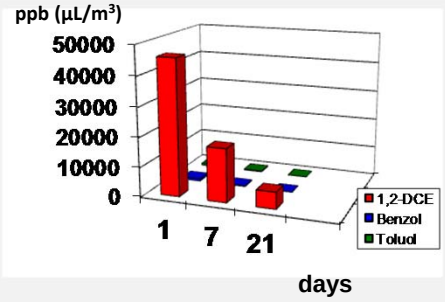
3/4. Study in Hamburg (additional 53+1000 random samples)

Fahrenholtz S, Hühnerfuss H, Baur X, Budnik LT. J Chromatography A 2010,
Fahrenholtz et al., in preparation

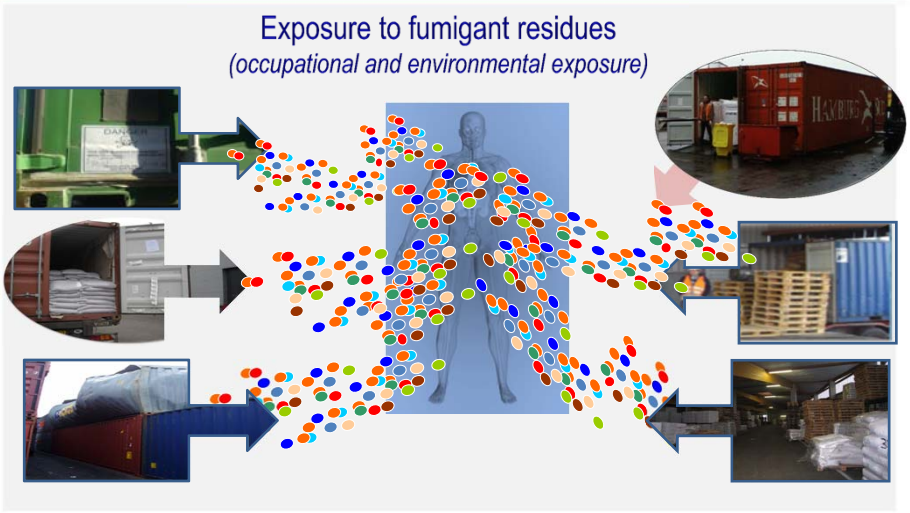
Industrial chemicals found:
Solvents and fumigant additives
(high concentrations)

benzene
toluene
ethyl benzene
dichloromethane
tetrachloromethane

Off gassing from container transported products
Example
Toys: (doll‘s playhouse)



- **Container and other transport units are un-loaded deep within the country sides outside the harbour areas (*those un-loading are often migrant workers, without medical support or coverage*)**
- **Workers and Bystanders can be exposed to fumigant residues in storage rooms**



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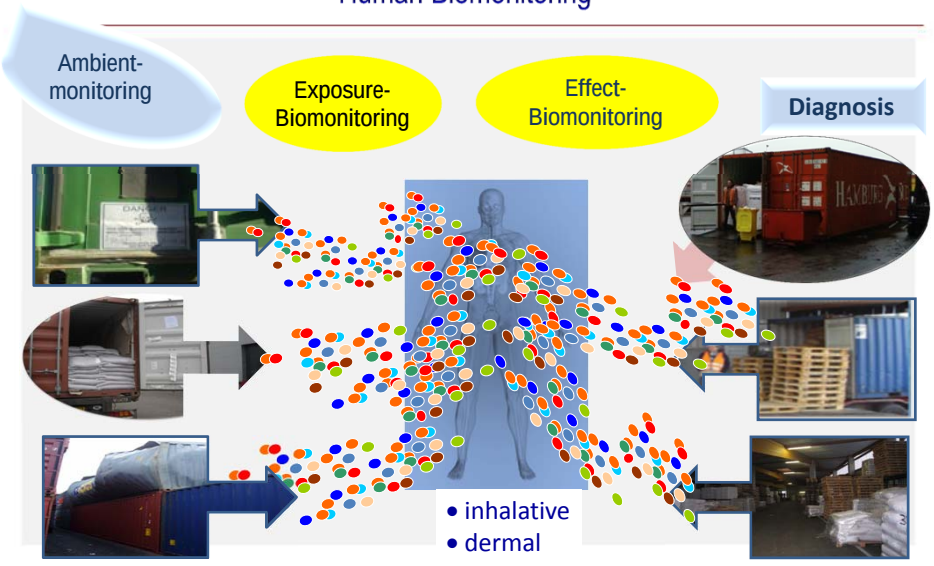
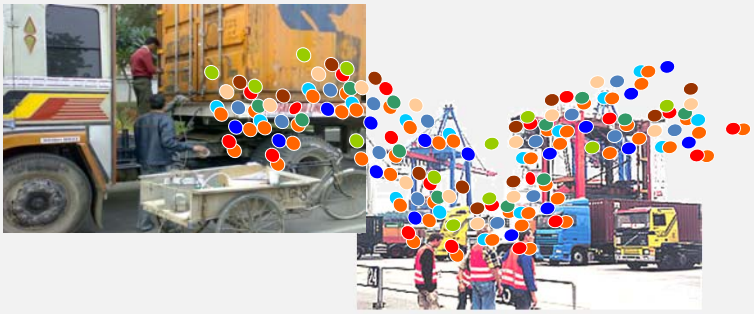
How to detect exposure?

Human Biomonitoring



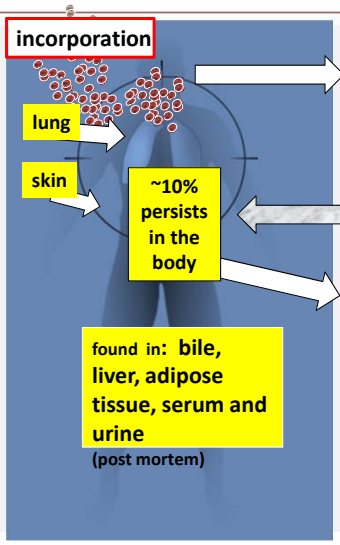
Major problem: *sampling time*



Short-term high exposure symptoms: (latency period of 2-48 h -3 days)

- Central nervous system depression, neuropsychiatry abnormalities (**headache, nausea, dizziness**)
- Inflammation of the bronchi and lung, Pulmonary edema (**flu like symptoms, phlegm, chest pain, shortness of breath**)

Exposure to methyl bromide



elimination

lung
(exhalation MeBr/ CO_2) **~40%**

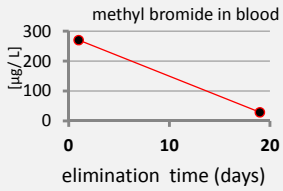
biotranformation in the liver (i.e. GST/ CYP)

kidneys
(elimination in urine) **~40%**

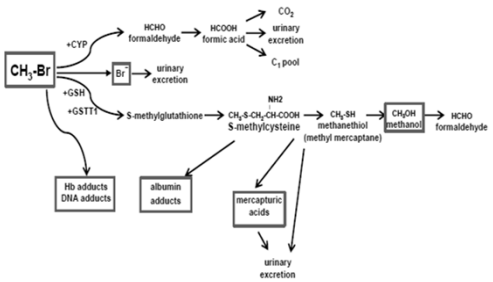
Budnik LT, Kloth S, Velasco-Garrido M, Baur X. Environ Health (2012)

Only extremely high concentrations can be detected late

Max. elimin. time described



Usually
1-3 days after exposure possible



Budnik LT, Kloth S, Velasco-Garrido M, Baur X. Environ Health (2012)

Own study: 164 individuals with presumed intoxication to fumigants, plus 30 controls).

78% male and 22% female subjects at median age of 44; 66% smoker, 34% non-smoker

The exposure assessment was performed with human biomonitoring (methyl bromide, ethylene dichloride, dichloromethane, other halo-alkanes).

Ambient-monitoring

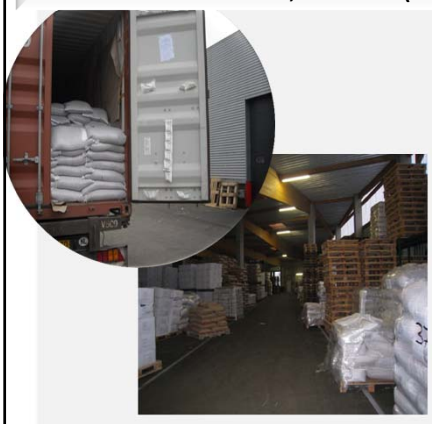
Exposure-Biomonitoring

Effect-Biomonitoring

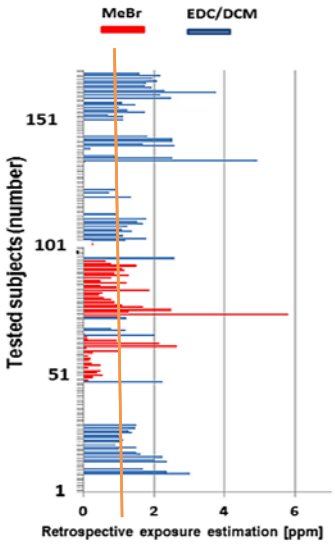
Diagnosis

86 patients with confirmed exposures to halo-alkanes above the non-cancer reference doses (RfD), but (for many) lower than the occupational exposure limits

Published in: Budnik et al., PLoS ONE (2013)

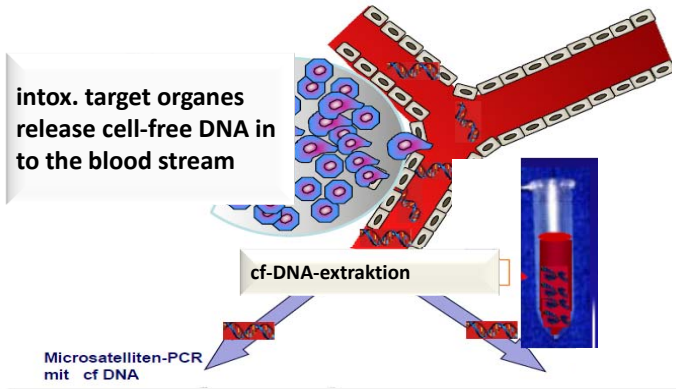


= legally applicable occupational exposure standards



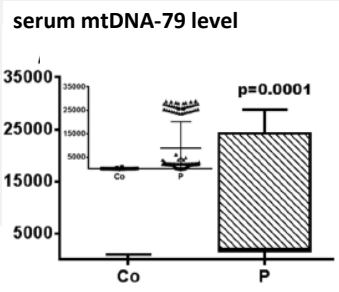
Mitochondrial DNA has a potential to serve as a biomarker recognizing vulnerable risk groups after exposure to toxic/carcinogenic chemicals

Published in: Budnik et al., PLoS ONE (2013)



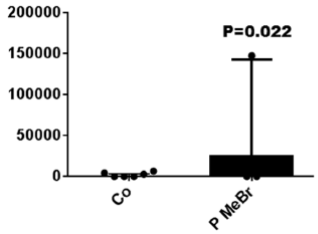
Enhanced cell free mtDNA levels in patients exposed to halogenated hydrocarbone pesticides (methyl bromide)

serum mtDNA-79 level



Exposed vs Controls

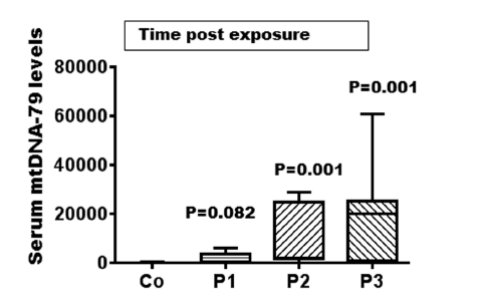
serum mtDNA-79 level



MeBr exposed vs Controls

Published in: Budnik et al., PLoS ONE (2013)

The relative amounts of mtDNA-79 in serum were positively associated with the lag-time after intoxication of these chemicals (r=0.99, p<0.0001).



Patient subgroups
P1 current intoxication
P2 short-term past exposure (weeks, up to 4 months)
P3 long-term past exposure (interim time at least 5 months)

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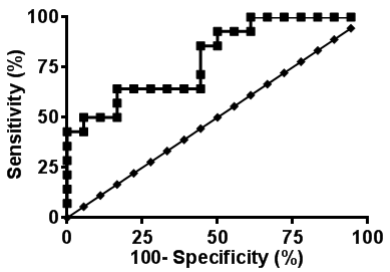
Serum mtDNA-79 level



The specificity for this biomarker increased from 30% to 97% several months post-exposure in patients with intoxication symptoms.

Patient subgroups
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Case report

European medium size company Importing electronic construction parts from south america and south east asia.

6 storage room workers were un-packing wooden pellets and/ or paper boxes covered with plastic containing with construction parts)

3 Workers were claiming on:

- **itchy skin**
- **very red eyes**
- **headache**
- **pins and needles in the legs**
- **dizziness**
- **breathing difficulties**
- **increasing irritability**

Patients
1. f, ns
2 f, s +
3, m, s++
4, f, s+
5, f, s++
6, m,ns

Long lag time post exposure

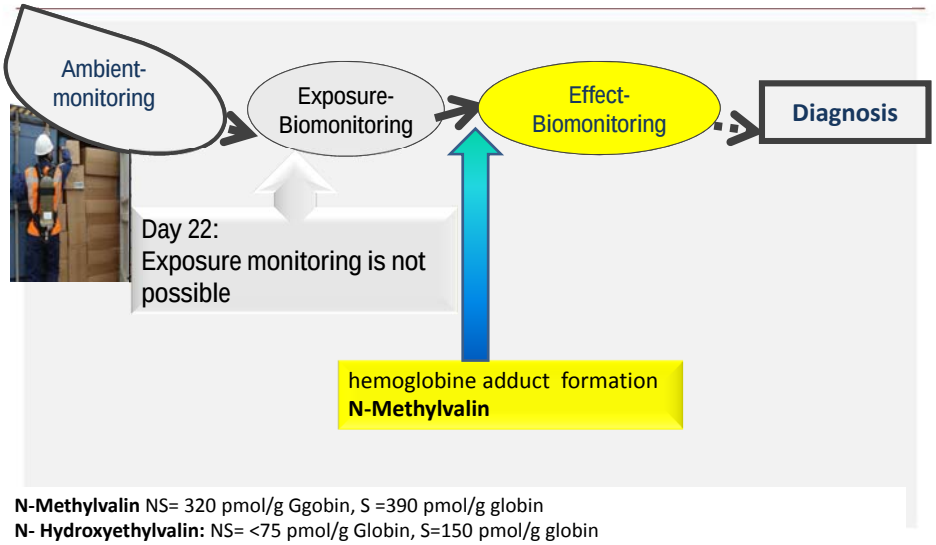
Governmental industrial hygienist is taking air samples

Results:
2.5 ppm-200 ppm methyl bromide

Day 2
Industrial physician is collecting blood samples (Serum/EDTA-Blood, NaF-Blood,Urine) and send samples to the commercial clinical chemistry laboratory to proof for the intoxication parameter)

No bromide or methyl bromide measurements or measurements for other intoxication parameter were performed
(Only differential blood picture was performed, the samples were destroyed)

It is still possible to extrapolate the exposure from the hemoglobin adduct levels (for accidental exposures)



N-Methylvalin NS= 320 pmol/g Ggobin, S =390 pmol/g globin
N- Hydroxyethylvalin: NS= <75 pmol/g Globin, S=150 pmol/g globin

Existing problems in many small or medium size companies through Europe

- **no risk assessment**
- **no (or not sufficient) air measurements (no correct measurements performed)**
- possible intoxication after chronic exposure from off gassing products, packing materials in storage facilities **Is not considered!**
- **No human biomonitoring samples collected to confirm the exposures** (or wrong sampling time, wrong matrixes, wrong samples etc.)
- Destroying valuable human sample in the clinical chemistry labors

Conclusions

In an emergency, appropriate protection measures can be undertaken only if the type of chemical that has been released is known precisely.

<u>Personal air samples</u> should be taken along the supply chain, e.g. when unloading the containers for reloading at harbor ports and <u>human-biomonitoring should be performed for vulnerable groups</u>.

Contribution
Co-workers & Research Partners

- Charite-Institute for Occupational Medicine, University Medicine, Berlin, Germany
  - Prof. Dr. Xaver Baur
- Institute for Occupational and Maritime Medicine, Universicty Medical Center Hamburg-Eppendorf, Hamburg, Germnay
  - Dr. Svea Fahrenholtz
  - Dr. Stefan Kloth
  - Dr. Alexandra M. Preisser
  - Sabrina Gadau, Msci
  - Bernd Poschadel
  - Susann Finger
  - Henry Vlceck
- Institute for Tumorbiology, University Medical Center, Hamburg, Germnay
  - Ass. Prof. Heidi Schwarzenbach
  - Bettina Steinbach
- Customs Office Waltershoff, Hamburg, Germany
- Arsence Analytics, Research and Development, Schwerin, germany (Dr. Andreas Walte)
- Frauenhofer Institute for Intelgent Systzems, St Augustin, Germany (Dr. Kobialka)
- Institute and outpatient Clinic for Occupationa, social and environmental Medicine, FA University Erlangen-Nürnberg, Germany (Prof. Göen)
- Dr. Schubert/ Dr. Jungnikels, Federal Institute for Risk Assessment
- .....

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- BMBF-Project DEGENA
- BMBF Project OPTIMA

Bundesministerium für Bildung und Forschung

- E&G Roggenbuck Foundation
- Hamburg Foundation for Fight Against Cancer
- State Department for Health and Consumer Protection, Hamburg
- Ministerie van Infrastructuur en Milieu, the Netherlands
- Federal Institute for Risk Assessment, Berlin

The Study is a part of WHO Global Plan of Action project :
New chemical health risks in transportation and warehousing due to the process of globalization