Incident preparedness – identification of chemicals suitable for human biomonitoring

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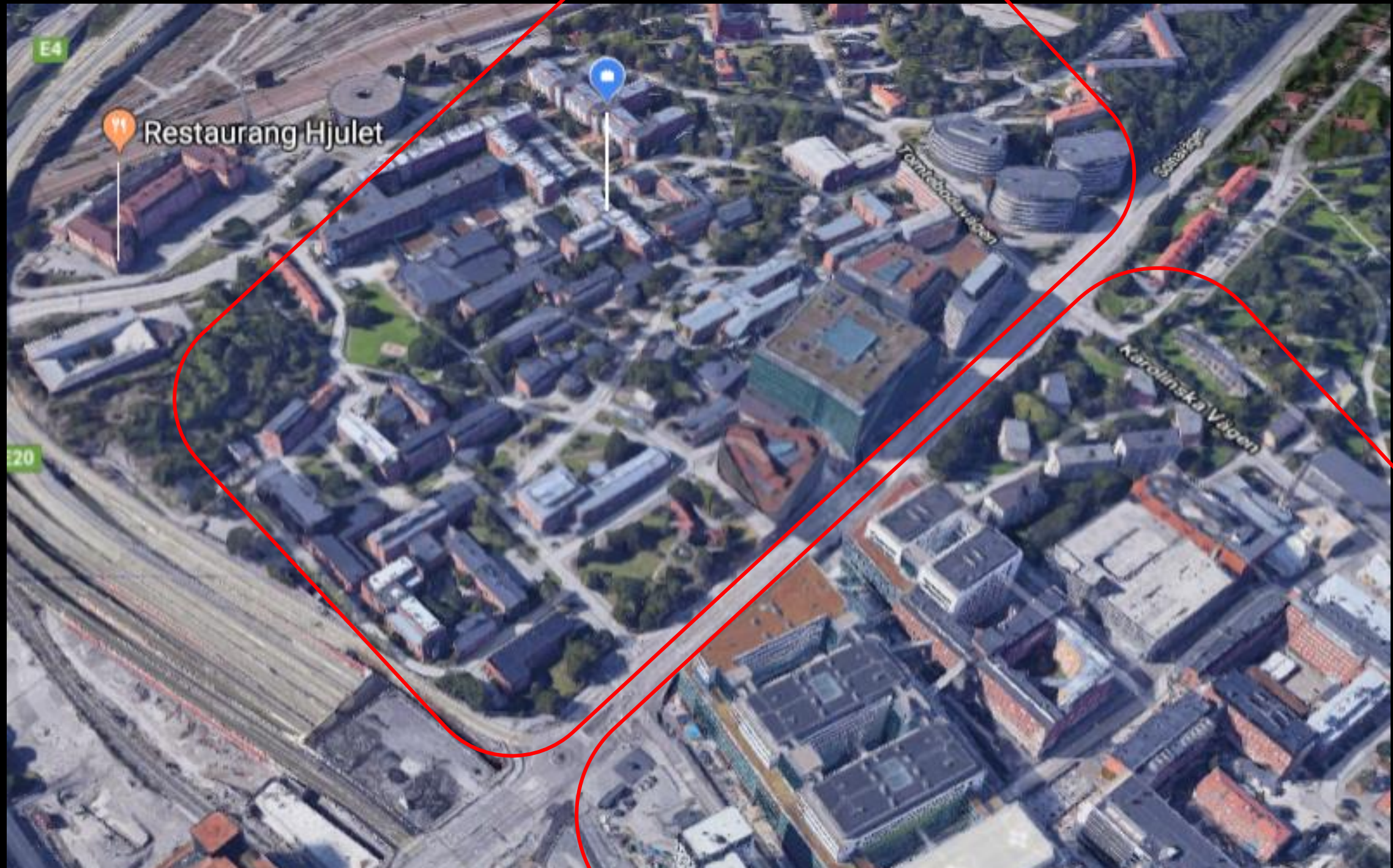
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Karolinska Vägen

Unit of Integrative Toxicology

Formerly Work Environment Toxicology

Human studies

- Acute effects
- Toxicokinetics, PBPK modelling, biomonitoring

3R-oriented research

- Dermal uptake
- Zebrafish embryos
- Human bronchial and alveolar epithelial cell cultures

Risk assessment

- Committees: Nordic Expert Group, EU SCOEL, , EU-LCI, US AEGL, US EPA, US NAS etc
- Research on risk assessment and limit setting

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Outline

- Workplace biomonitoring in Sweden (briefly)
- Environmental human biomonitoring in Sweden (briefly)
- Incidence preparedness - I dentification of chemicals suitable for HBM
  - Swedish priority substances
  - For which could BM be used?
  - Importance of toxicokinetics & half time
- Near(?) future biomarkers (briefly)
  - Wildfires
  - Breath monitoring of cyanide poisoning
  - Effect biomarkers for reactive/oxidative gases
- Conclusions

Workplace biomonitoring in Sweden

Cadmium

Lead

Provisions on medical check-up, biological limits, data storage etc

Biomonitoring mentioned as possibility

Mercury
Arsenik
Chromium
Carbon monoxide
Fluorides

Benzene
Cyanide
Diisocyanates
Methylisocyanate (MDI)
Nicotin
N-Methylpyrrolidone (NMP)

PAHs
Phtalic anhydrides
Phosphate esters
PCB
Styrene
Xylenes

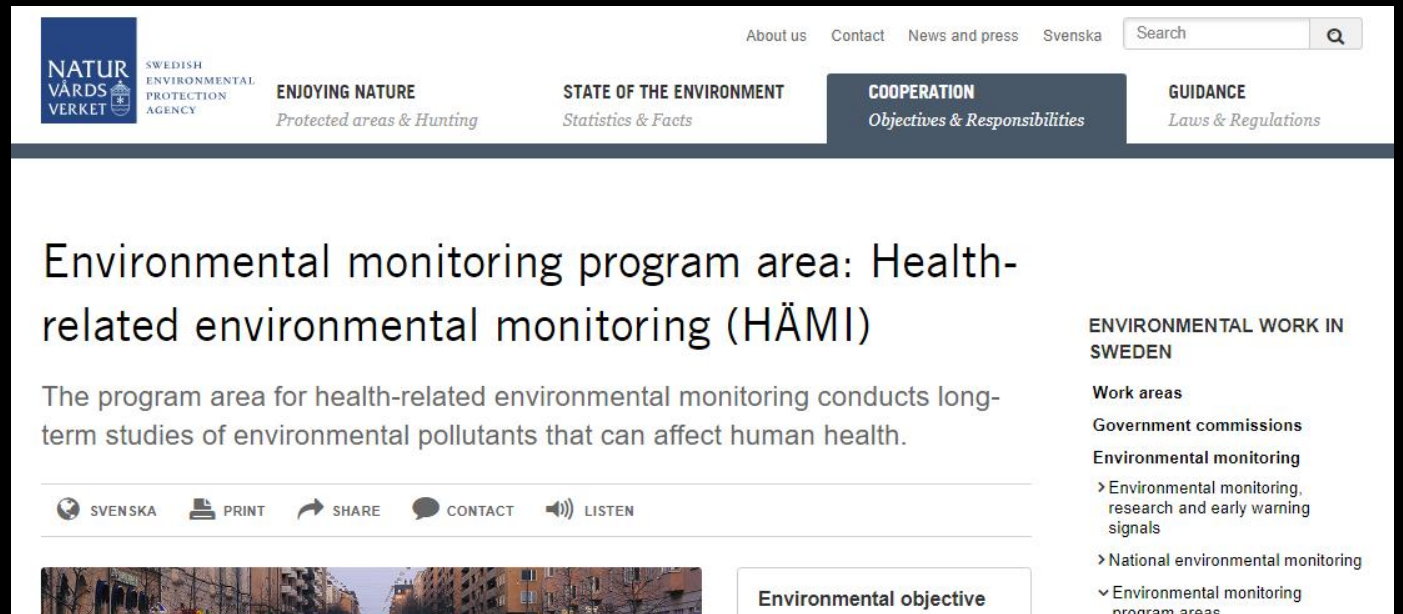
Environmental human biomonitoring in Sweden

Part of the Swedish health-related environment monitoring program (HÄMI)

Focus on population long-term environmental exposure

Project based, some long-term trends

Data compiled at the IMM and the Swedish EPA



Examples:

Bisphenols

Cadmium

Cotinin

Flame retardants

Lead

Mercury

Nonylphenol

Parabens

PCBs

Perfluorinated compounds (PFAS)

Persistent organic pollutants (POPs)

Phtalates, plasticizers

Triclosan etc

Swedish priority substances for incident preparedness

Most important industrial chemicals of concern for

- risk and vulnerability analyzes
- emergency preparedness
- enhancement measures

We identified chemicals used in Sweden that could (if released in air) acutely and severely affect many people’s health, and therefore be a burden on society's rescue organizations and health care system

Swedish priority substances

Chemicals selected from combined analysis

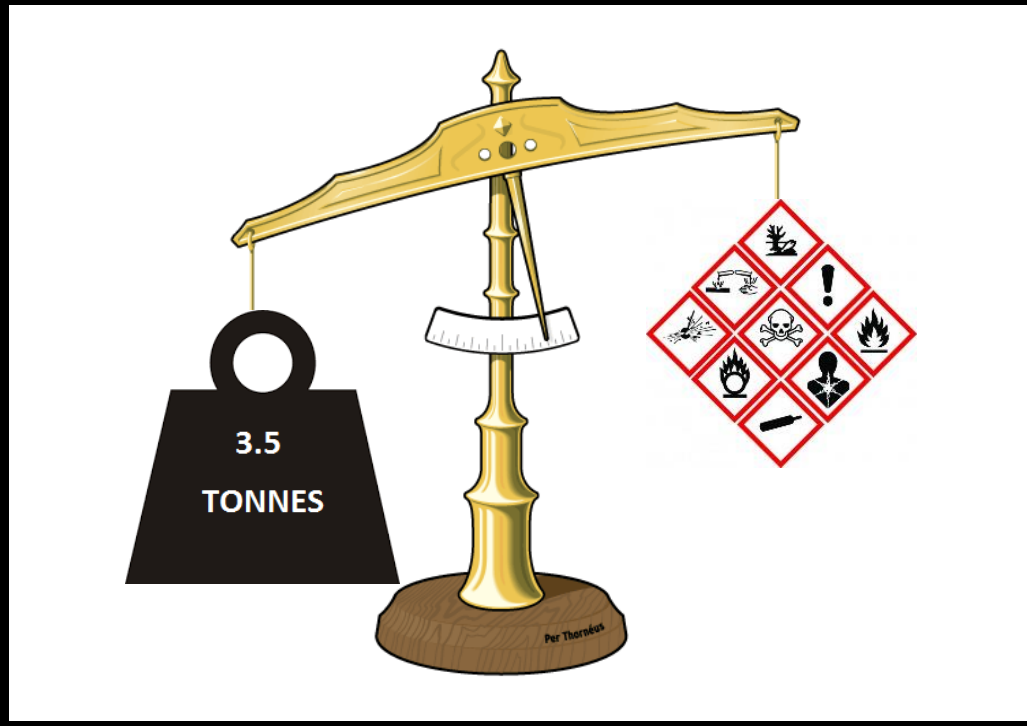
- volume tonnes per year in Sweden 2012-2014
- chemical-physical properties

  volatility/vapor pressure/boiling point

  reactivity with water resulting in toxic products
- nature and severity of toxicity

≈ 83 substances identified

Not addressed: Possibility to monitor in air or by HBM



Limitations

- Contamination of ground or ground water not considered
- ”Slowly acting” chemicals not considered
  Because not expected to cause an immediate strain on the rescue organizations and health care system even if the might be highly persistent, bioaccumulating and cause long-term health effects
- Still, the list may help identify priority areas for HBM preparedness in accidents and disasters

Why biomonitoring in incidences and disasters ?

- People are worried: “How much was I exposed?”
- Reverse dosimetry - Basis for follow up studies on cancer and other long-term effects
- Basis for triage and acute treatment

Swedish priority substances
Exposure biomonitoring not likely useful

[ebm] Effect biomarkers possible?
[H] Skin

Examples:

Ammonia
Boron trifluoride
Bromine[ebm]
Chlorine[ebm]
Chloroacetic acid[H]
Formic acid
Hydrogen chloride
Hydrogen peroxide[ebm]
Nitric acid
Ozone
Phosphoric acid
Potassium hydroxide
Sulfuric acid
Sodium hydroxide

Swedish priority substances
Biomonitoring feasible but not readily available

Examples:

Acetonitrile[H]
Acrylic acid[H]
Allyl chloride[H]
Dimethyl disulfide[H]
Hydrogen cyanide and salts[H]
Phosphine, aluminium phosphide

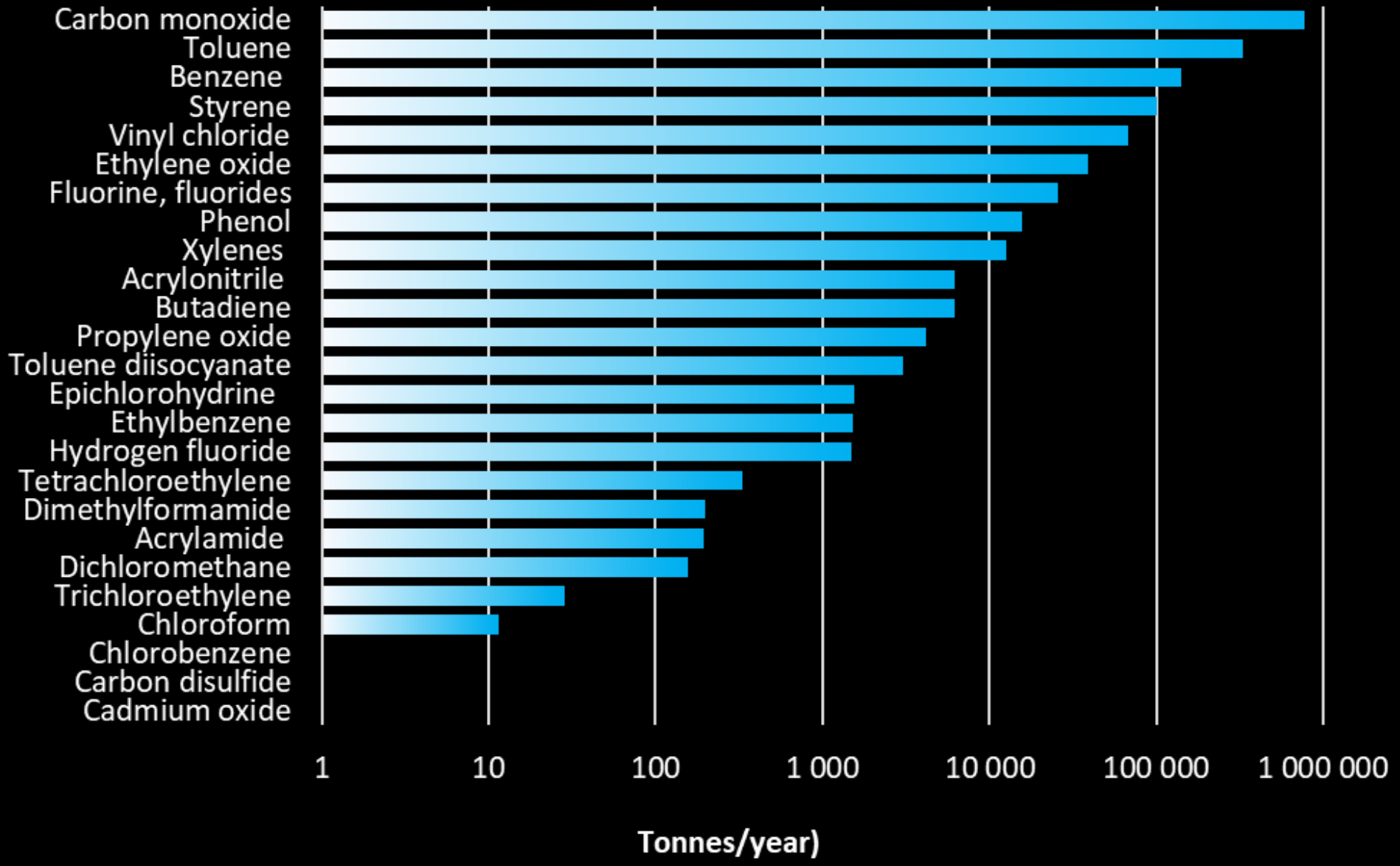
Swedish priority substances
Biomonitoring readily available

Available as German
BAT, ACGIH BEI, SCOEL
BLV and/or Hb adduct

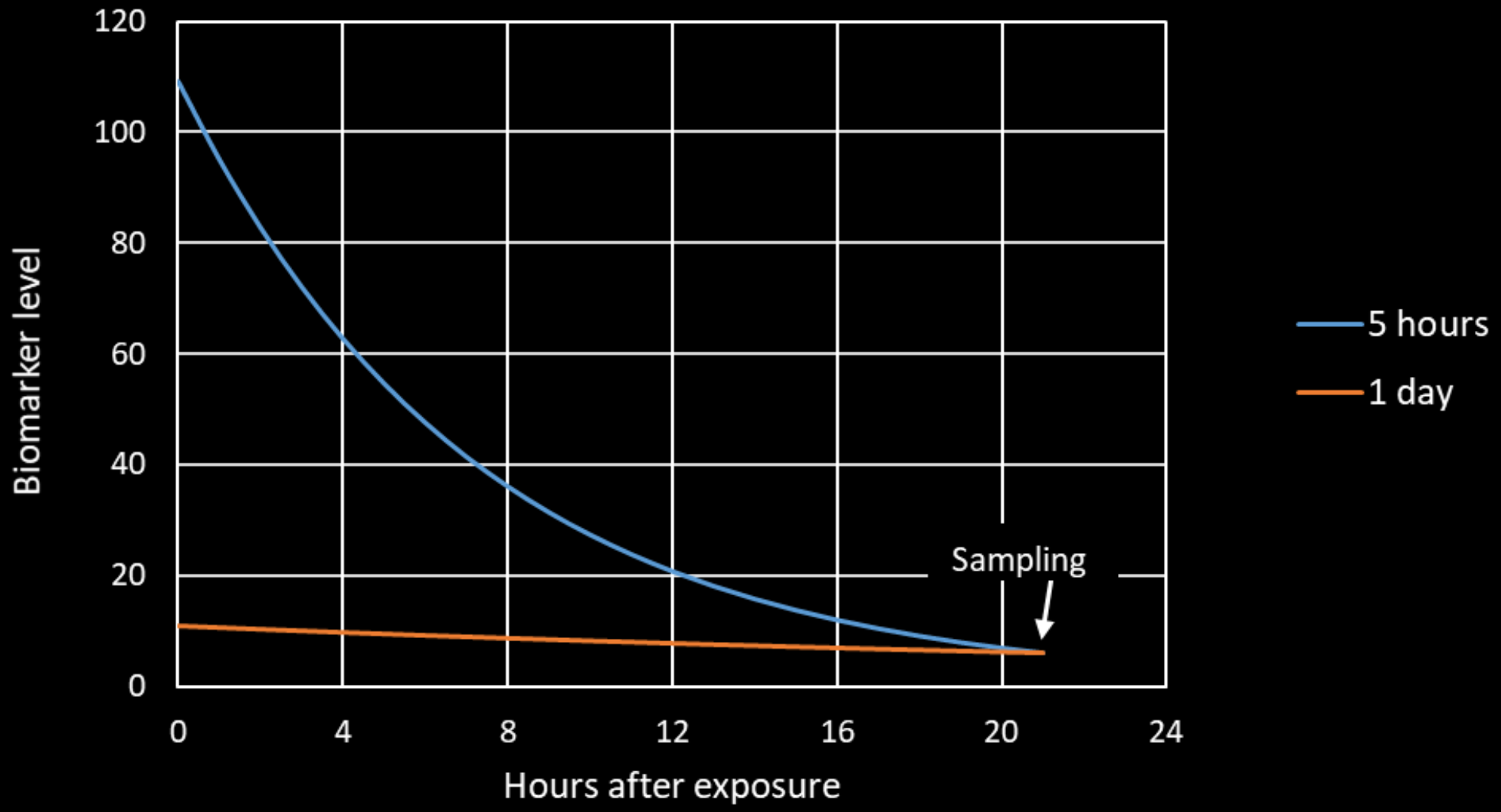
25 out of 83 (30%)

Acrylamide[H]
Acrylonitrile[H]
Benzene[H]
Butadiene
Cadmium oxide
Carbon disulfide[H]
Carbon monoxide
Chlorobenzene
Chloroform[H]
Dichloromethane[H]
Dimethylformamide[H]
Epichlorohydrine[H]
Ethylbenzene[H]
Ethylene oxide[H]
Fluorine
Hydrogen fluoride
Phenol[H]
Propylene oxide
Styrene[H]
TDI[H]
Tetrachloroethylene
Toluene[H]
Trichloroethylene
Vinyl chloride[H]
Xylenes[H]

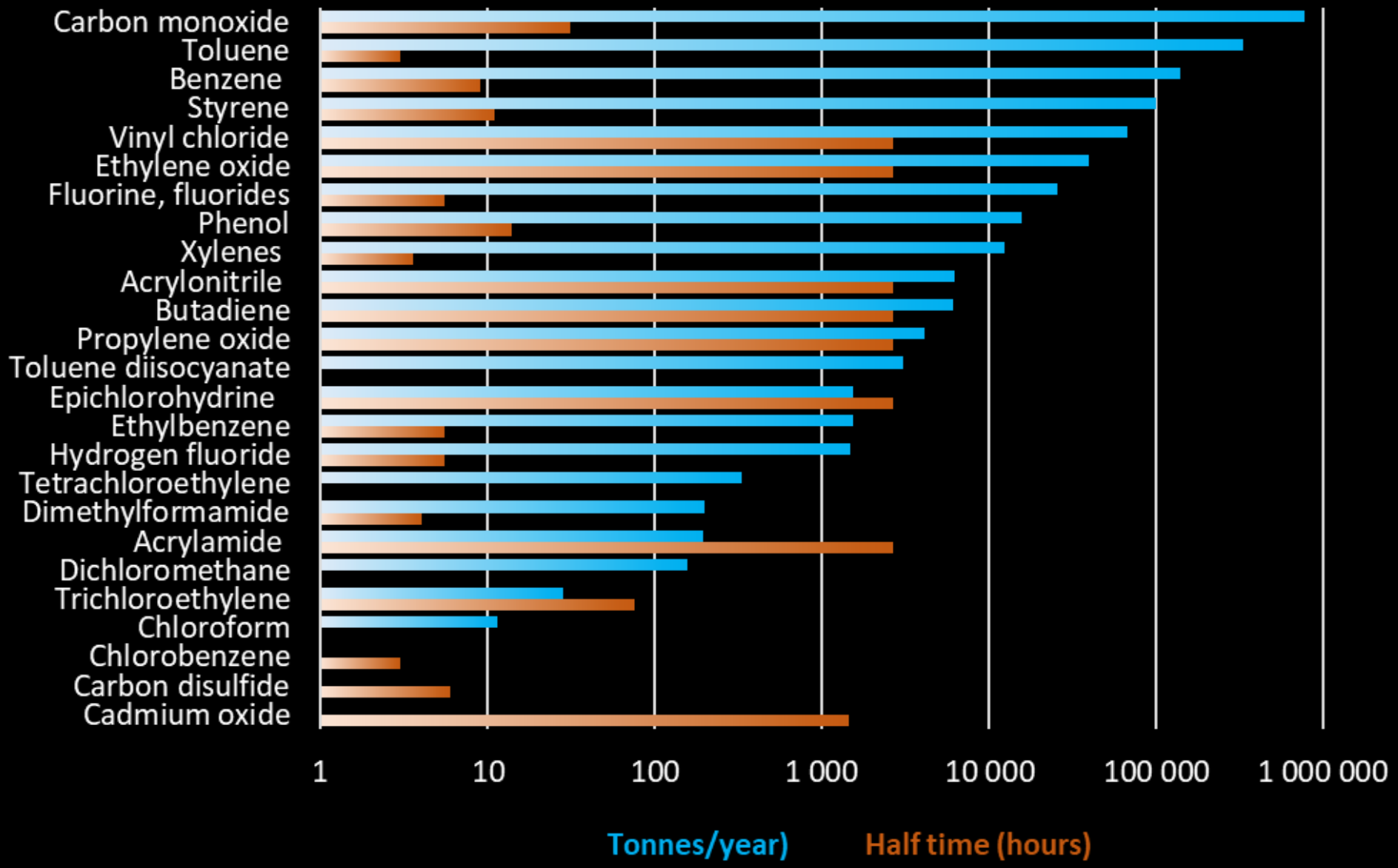
Swedish priority substances with biomonitoring method – annual use



Knowledge of toxicokinetic profile and time of exposure and sampling are keys to reverse dosimetry (retrospective exposure assessment)



Swedish priority substances with biomonitoring method - annual use and biomarker half times



Wildfires

Massive increase in pollutants of ”natural origin”…

- Volatile organic compounds (VOC) such as BTEX and aldehydes
- Semivolatiles (sVOC) such as PAH

…and of ”human origin”

- Heavy metals
- Fire retardants
- HCl, SO_2, HF
- Pesticides, etc

Recent meta analysis of firefighters found excess risks for cancers of the colon, rectum, prostate, testis, bladder, thyroid and pleura and for malignant melanoma and Non-Hodgkin’s lymphoma

Jalilian, Int J Cancer, 2019

Breath monitoring of cyanide poisoning

Lethal HCN levels formed when nitrogen-containing material burn

Many fire victims primarily die from HCN, not CO

Our studies suggest that breath HCN is significantly elevated in cyanide poisoning…

…and that this HCN has systemic origin

No convenient method for HCN in breath at present

Papers by Stamyr, Johanson et al:
- HCN washout kinetics in breath, Toxicol Lett 2008
- HCN background levels in breath, Biomarkers 2009
- Forensic data on HCN and CO, Inhal Toxicol 2012
- PBPK model for HCN, Arch Toxicol 2015

Effect biomarkers for reactive/oxidative gases

	Tons/y in Sweden	Potential biomarker	Rat/Mouse, Reference
Chlorine	67	Chlorinated lipids (exposure markers) Nitric oxide 8-Isoprostane (markers of oxidative stress)	R, Hemström, Anal Chem, 2016 M, Ford, J Lipid Res 2016 R, Lu, Toxicol, 2014 R, Elfsmark, Tox Lett, 2018

Conclusions

- Our recent investigation on Swedish priority substances should be useful also to set priorities for HBM in incidents and disasters
- HBM method readily available for 25 (one third) of the priority substances
- 8 have long-lived biomarkers (mainly Hb adducts) or are easy to measure in the field (COHb / breath CO)
- Uptake via skin may be significant for many (16 of 25), an additional reason for biomonitoring

Conclusions

Start with these

- HBM method readily available for 25 (one third) of the Swedish priority substances
- Fast response is crucial
- Action should be taken to improve preparedness
- Readily available instructions
  - How, where and when to sample, importance of timing
  - Sample treatment, storage conditions
  - What to record: sampling time, location of subject
  - Where to send for analysis, brief info on analytical method
  - How to interpret results, toxicokinetics, toxicity
  - Patient treatment (if applicable)

Swedish Poison Information Center already has much info