Exposure Science Research at the JRC Institute for Health and Consumer Protection

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Policy needs for health and safety data:

Consumer Policy and REACH: need for data on chemical safety of consumer products and on aggregate exposure

Env & Health Action Plan: Address mixture effects/Indoor air

Food safety: safety of chemicals in FCM/foodstuff

Methodological Problems linked to:

- Complexity of exposure pathways
- Cocktail (beyond additive) effect of mixtures
- Dose extrapolation
- Integrated use of exposure data (incl. human epidemiological and biomonitoring data)
JRC involvement

International collaborative research projects:
- HEIMTSA (Integrated Health Impact Assessment Toolbox)
- 2-FUN (Health Risk Assessment for Future Scenarios)
- HENVINET (Health and Environment Network)
- CAIR4HEALTH (Air quality and Health)
- HEREPLUS (Health Risk from Environmental Pollution Levels in Urban Settings)
- GENESIS (Generic EU Sustainable Information Space for Environment)

In-house projects:
- Human Exposure Data Centre (with EEA)
- Biology based dose-response modeling
- Toxicogenomics for mixture toxicity assessment and exposure/effect biomarker identification
Challenges for Exposure Science

• Plethora of analytical/monitoring data
• 30-100,000 chemicals in the market

In the European Union:
• REACH introduces exposure-based waiving of toxicity testing
• REACH uses exposure surrogates: market volume p.a.
• Very ambitious time plan for evaluating risk of 30,000 chemicals
• E&H action plan: poses the problem of chemical mixtures and of susceptible population groups
• Adequate support of green chemistry towards the Sustainable Development goals
• Increased public awareness of risks of chemicals
• Need to set priorities for efficient risk assessment of chemicals
• The most plausible avenue/greatest challenge is to link all available data, incl.:
  - environmental
  - human biomonitoring
  - “sentinels”
  - surrogates
How we can optimize exposure assessment of chemicals?

A Holistic Approach is needed, regarding:

**Full chain assessment**
- Sources-emissions
- Media concentrations
- Personal exposure
- Internal dose
- Biology Based Dose Response

**Methodological tools exploitation**
- Measurements data
  - environmental parameters
  - concentrations
  - personal exposure
  - biomonitoring
- Toxicity testing
  - animal data
  - gene expression and other omics
- Epidemiological data
- Clinical data

How can we connect all these elements?

A single-word answer: the Exposome
Toward Exposure Biology, through modelling and data assimilation

“Systems Biology” Approach

“Physiome” Approach

Physiologically Based Pharmacokinetic (PBPK) Models
Exposure Science Community of Practice Seminar, September 8, 2009

**Integrated Multi-layer computational Approach**

- **Characterization of Exposure Factors**
- **Aggregate and Cumulative Exposure Models**
- **Probabilistic Exposure**

**Exposure Biology**

- **Biologically Effective Dose**
  - Early Biological Effects
- **Dose–Effect Models**
- **Biomarkers of exposure and effects**

**Expressomics**

- **Individual Profiles**
  - Life Styles
  - Polymorphisms
- **Individual Response**
- **Biomarkers of individual Susceptibility**

**Population Studies**

- **Molecular Dosimetry**
- **Assessment of Risk Factors**
Tool Development
Exposure Science Community of Practice Seminar, September 8, 2009

Full chain exposure assessment

Platform components

$$C(x, y) = \frac{q}{\pi \sigma u} \int_{y-x}^{y-x} \exp \left( -\frac{y^2}{2\sigma^2} \right) dy$$

$$C_I = \sum f_n \cdot C_n$$

$$V_i \frac{dC_I}{dt} = Q_i (C_I - CV_a) - \text{Metab}_I - \text{Elim}_I + \text{Amp}_{I, I} - \text{Pr Binding}_I$$

$$P(y) = 1 - \exp(ay + by^2 + cy^4)$$

MCMC simulation in all stages
Generic PBTK model

General formula describing ADME:

\[ V_i \frac{dC_{ij}}{dt} = Q_i (CA_j - CV_{ij}) - Metab_{ij} - E\text{lim}_{ij} + Absorp_{ij} - Pr\ Binding_{ij} \]

Absorption
Distribution
Metabolism
Elimination

Tissue characteristics that affect the internal concentrations are:
• Blood flow
• Perfusion
• Protein binding
• Metabolic and elimination activity
Expressomics for the Exposome

Experimental Design

Tissues RNA
Mice, Rats, Humans

Whole Genome Discovery
Systems
(32,000 genes)

Gene Identification

Validation by Quantitative PCR

BIOINFORMATICS

Environment and Health
Signature of chemicals in products
Implementation of Risk Assessment

Biomarkers and
Systems Toxicology
Models

Integrated approach
with
Proteomics/Metabonomics

Genes Modulation
Genes Classification
Genes Pathway

Statistical Evaluation
Human Biomonitoring

Early diagnosis of cardiovascular disease associated with exposure to chemicals through analysis of metabolites can be used for easy, non-invasive monitoring of health effect indicators.

Biomarkers of exposure and effects

The difference in susceptibility to chemical exposure between males and females was demonstrated by analysis of the whole genome in cell lines and tissues exposed to mixtures of chemicals.

By identifying the difference in gene expression we can have early warning about anticipated health effects.
Chemical Mixtures – Cumulative Exposure
Chemical mixtures: molecular fingerprinting

**Milan Outdoor Air Mix**

**Fly Ash**

**Indoor Air Mix**

Regulated genes, FC ± 2

<table>
<thead>
<tr>
<th></th>
<th>total genes</th>
<th>up</th>
<th>down</th>
</tr>
</thead>
<tbody>
<tr>
<td>Milan Air Mix</td>
<td>376</td>
<td>209</td>
<td>167</td>
</tr>
<tr>
<td>Fly Ash</td>
<td>145</td>
<td>92</td>
<td>53</td>
</tr>
<tr>
<td>Indoor Air Mix</td>
<td>214</td>
<td>66</td>
<td>148</td>
</tr>
</tbody>
</table>
Comparative Cluster Analysis between Ha-CaT and A549 exposed to Air Mixtures
IAM: red
Aromatics: green
Aldehydes: orange
Terpenes: blue

Yellow: components in more than one treatment
Oxidative stress pathway
Environmental exposure: in-/outdoor/personal

AIRMEX Project
Sites of measurement campaigns

- Personal exposure
  - Benzene
  - Toluene
  - Xylene
  - Ethylbenzene

- Indoor concentration
  - Benzene
  - Toluene
  - Xylene
  - Ethylbenzene

- Outdoor concentration
  - Benzene
  - Toluene
  - Xylene
  - Ethylbenzene

Locations:
- Nijmegen 28.71
- Brussels 39.7
- Leipzig 29.04
- Milan 74.07
- Catania 73.51
- Thessaloniki 88.43
- Athens 86.11
- Nicosia 24.87

Values:
- Nijmegen 28.71
- Brussels 13.25
- Leipzig 6.84
- Milan 26.13
- Catania 48.04
- Thessaloniki 100.34
- Athens 69.52
- Nicosia 16.1
- Brussels 11.4
- Leipzig 21.08
- Milan 16.87
- Catania 38.35
- Thessaloniki 61.08
- Athens 59.32
- Nicosia 8.74
BTEX “in vitro” experiments

• Cells: A549
• Time of exposure: 4h and 24 h
• Doses: 10ng/L, 100ng/L, 10ug/L

Mixture A:

• 20% Benzene
• 40% Toluene
• 10% Ethylbenzene
• 30% Xylene

Mixture B:

• 10% Benzene
• 60% Toluene
• 10% Ethylbenzene
• 20% Xylene

BTEX “in vivo” experiments

• Tissue: Mouse Lung after i.tr.
• Time of exposure: 4h and 24 h
• Dose: 10 ug/L (=250ng/Kg)
Number of modulated genes by different mixtures (A and B) in A549, 4h and 24 h, 2FC
Biological processes (p-value ≤0.01), BTEX in A549 cells, Mix A and Mix B, 4h
Biological processes (p-value ≤ 0.01), BTEX in A549 cells, Mix A and Mix B, 24h
Apoptosis Signaling Pathway – BTEX, Mouse Lung (i.t.)

4h

24h
Benzene metabolism

Benzene oxide

Epoxide hydrolase

Non enzymatic rearrangement

Dihydrodiol dehydrogenase
PBPK Model for Benzene (with Metabolism)
Lyapunov exponent: system stability

If $\lambda > 1$ the system is chaotic and unstable

$\lambda$ measures the sensitivity of the system to its initial conditions

If $\lambda < 1$ the system is attracted to a stable point or a stable periodic trajectory (limit cycle). This is a non-conservative condition. The absolute value of $\lambda$ is a metric of system sensitivity

If $\lambda = 1$ the system is stable, conservative and at steady state

$\lambda_{BTEX} < 1$ Unstable system
Biological system dynamics: emergence of limit cycles

Through phase space analysis unstable attractors like limit cycles are identified. The system is inherently meta-stable.
Increment in maximum bone marrow concentration of benzene for exposition to different mixtures of BTEX.
Health endpoint-triggered exposure assessment

4-(N-nitrosomethylamino)-1-(3-pyridyl)-1-butanone (NNK)

Benzene

Formaldehyde

Lung cancer

Leukemia

Nasopharyngeal cancer
Benzene, NNK, Formaldehyde metabolism – DNA adducts formation

Benzene

- Benzene oxide
  - Phenol
  - Hydroquinone
  - Benzene oxide DNA adduct

NNK

- NNK DNA adduct
- (S) NNAL
  - Gluc – (S) NNAL
  - (R) NNAL
  - Gluc – (R) NNAL
- NNK DNA adduct

Formaldehyde

- Formaldehyde DNA adducts
Average values of major smoke constituents in the sidestream smoke of 12 commercial cigarette brands assayed in the 1999 Massachusetts Benchmark Study using Massachusetts smoking parameters (IARC, 2004)

<table>
<thead>
<tr>
<th>Constituent</th>
<th>Unit</th>
<th>Range</th>
<th>SS/MS ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ammonia</td>
<td>mg/cig.</td>
<td>4.0-6.6</td>
<td>147</td>
</tr>
<tr>
<td>1-Aminonaphthalene</td>
<td>ng/cig.</td>
<td>165.8–273.9</td>
<td>7.10</td>
</tr>
<tr>
<td>2-Aminonaphthalene</td>
<td>ng/cig.</td>
<td>113.5–171.6</td>
<td>8.83</td>
</tr>
<tr>
<td>3-Aminobiphenyl</td>
<td>ng/cig.</td>
<td>28.0–42.2</td>
<td>10.83</td>
</tr>
<tr>
<td>4-Aminobiphenyl</td>
<td>ng/cig.</td>
<td>20.8–31.8</td>
<td>5.41</td>
</tr>
<tr>
<td>Benzo[a]pyrene</td>
<td>ng/cig.</td>
<td>51.8–94.5</td>
<td>3.22</td>
</tr>
<tr>
<td>Formaldehyde</td>
<td>µg/cig.</td>
<td>147.4–967.5</td>
<td>14.78</td>
</tr>
<tr>
<td>Acetaldehyde</td>
<td>µg/cig.</td>
<td>683.7–2586.8</td>
<td>1.31</td>
</tr>
<tr>
<td>Acetone</td>
<td>µg/cig.</td>
<td>451.3–1204.8</td>
<td>1.52</td>
</tr>
<tr>
<td>Acrolein</td>
<td>µg/cig.</td>
<td>342.1–522.7</td>
<td>2.53</td>
</tr>
<tr>
<td>Benzene</td>
<td>µg/cig.</td>
<td>71-134</td>
<td>0.8</td>
</tr>
<tr>
<td>Propionaldehyde</td>
<td>µg/cig.</td>
<td>118.4–267.6</td>
<td>1.06</td>
</tr>
<tr>
<td>Crotonaldehyde</td>
<td>µg/cig.</td>
<td>62.2–121.8</td>
<td>1.95</td>
</tr>
<tr>
<td>Butyraldehyde</td>
<td>µg/cig.</td>
<td>138.0–244.9</td>
<td>2.68</td>
</tr>
<tr>
<td>Hydrogen cyanide</td>
<td>mg/cig.</td>
<td>0.19–0.35</td>
<td>0.77</td>
</tr>
<tr>
<td>Mercury</td>
<td>ng/cig.</td>
<td>5.2–13.7</td>
<td>1.09</td>
</tr>
<tr>
<td>Nickel</td>
<td>ng/cig.</td>
<td>ND–ND</td>
<td></td>
</tr>
<tr>
<td>Chromium</td>
<td>ng/cig.</td>
<td>ND–ND</td>
<td></td>
</tr>
<tr>
<td>Cadmium</td>
<td>ng/cig.</td>
<td>122–265</td>
<td>1.47</td>
</tr>
<tr>
<td>Arsenic</td>
<td>ng/cig.</td>
<td>3.5–26.5</td>
<td>1.51</td>
</tr>
<tr>
<td>Selenium</td>
<td>ng/cig.</td>
<td>ND–ND</td>
<td></td>
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<tr>
<td>Lead</td>
<td>ng/cig.</td>
<td>2.7–6.6</td>
<td>0.09</td>
</tr>
<tr>
<td>Nitric oxide</td>
<td>mg/cig.</td>
<td>1.0–1.6</td>
<td>2.79</td>
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<td>Carbon monoxide</td>
<td>mg/cig.</td>
<td>31.5–54.1</td>
<td>1.87</td>
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<tr>
<td>‘Tar’</td>
<td>mg/cig.</td>
<td>10.5–34.4</td>
<td>0.91</td>
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<tr>
<td>Nicotine</td>
<td>mg/cig.</td>
<td>1.9–5.3</td>
<td>2.31</td>
</tr>
<tr>
<td>Catechol</td>
<td>µg/cig.</td>
<td>64.5–107.0</td>
<td>0.85</td>
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<tr>
<td>Hydroquinone</td>
<td>µg/cig.</td>
<td>49.8–134.1</td>
<td>0.94</td>
</tr>
<tr>
<td>Resorcinol</td>
<td>µg/cig.</td>
<td>ND–ND</td>
<td></td>
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<tr>
<td>meta-Cresol + para-Cresol</td>
<td>µg/cig.</td>
<td>40.9–113.2</td>
<td>4.36</td>
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<tr>
<td>ortho-Cresol</td>
<td>µg/cig.</td>
<td>13.6–45.9</td>
<td>4.35</td>
</tr>
<tr>
<td>NNK</td>
<td>ng/cig.</td>
<td>69.8–115.2</td>
<td>0.43</td>
</tr>
</tbody>
</table>

Data necessary for the EU-27 scale estimation

- Smoking emissions (IARC)
- Smoking prevalence-population exposed to ETS (WHO)
- Time activity patterns
- Volumes of residences
- Indoor/outdoor air exchange rate

(EXPOLIS study)
Hierarchical population model used in Bayesian analysis (Bois et al., 1996).

Circles represent distributions and squares/rectangles represent known entities.

- $\mu$: prior mean distribution
- $\Sigma^2$: prior variance distribution
- $\theta$: study level distributions for each of the parameters based on randomly selected values for the mean and variance from the population distributions $\mu$ and $\Sigma^2$
EU-27 cancer risk estimations

Individual risk—Expected lifetime cases
Aggregate exposure
Formaldehyde indoor conc. (μg/m³)

- Max
- Average
- Min

Formaldehyde exposure
Formaldehyde exposure

Limit of observed biological responses

- MCMC simulation (Exposure+Biological parameters)
- MCMC simulation (Biological parameters only)

0% of the exposed population

0.1% of the exposed population

0.01% of the exposed population

Amount of population ($/10^6$)

DPX concentration (mM)
Aggregate exposure: the Benzene study

Exposure Science Community of Practice Seminar, September 8, 2009
**Activities time fraction**

Size: Exposure  
Color: ETS presence  
X axis: Fraction of time spend Outdoor  
Y axis: Fraction of time spend indoor  
Z axis: Fraction of time spend driving

<table>
<thead>
<tr>
<th></th>
<th>Unstandardized Regression Coefficient</th>
<th>Standardized Regression Coefficient</th>
<th>Significance (&gt;0.05)</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>Summer</td>
<td>Winter</td>
<td>Summer</td>
</tr>
<tr>
<td>Constant</td>
<td>3.1</td>
<td>2.3</td>
<td></td>
</tr>
<tr>
<td>Walking/Outdoor</td>
<td>-0.06</td>
<td>0.09</td>
<td>0.03</td>
</tr>
<tr>
<td>Driving</td>
<td>0.53</td>
<td>0.62</td>
<td>0.46</td>
</tr>
<tr>
<td>Ind. Loc. Zone 1</td>
<td>0.20</td>
<td>0.06</td>
<td>0.33</td>
</tr>
<tr>
<td>Ind. Loc. Zone 2</td>
<td>-0.04</td>
<td>-0.01</td>
<td>0.08</td>
</tr>
<tr>
<td>ETS presence</td>
<td>3.41</td>
<td>4.41</td>
<td>0.17</td>
</tr>
</tbody>
</table>
Active sampling measurements

Benzene concentrations (μg/m$^3$)

- Driving
- Walking/Outdoor
- Indoor

Percentage of observations (%)

- Driving
- Walking
- Indoor

Exposure (μg/m$^3$)

5 15 25 35 45 55 65
Regression exposure modelling

\[
E = \left( \frac{T_1}{T} \right) (11.1 + Sm \cdot 4.3 - Lz \cdot 4 - Tz \cdot 2.5 - Ws \cdot 0.6 + UB \cdot 1.3) + \\
\left( \frac{T_D}{T} \right) (36.5 + Wc \cdot 11.9 - Lz \cdot 14.8 - Tz \cdot 3.72 - Ws \cdot 0.001 + UB \cdot 2.5) + \\
\left( \frac{T_W}{T} \right) (22.2 - Lz \cdot 6.2 - Tz \cdot 1.1 - Ws \cdot 5.8 + UB \cdot 2)
\]

Sm: ETS presence (fraction 0 till 1)
Wc: Closed (1) or open (0) windows during driving
Lz: Location zone (1-3)
Tz: Time zone (1-4)
Ws: Wind speed (m/sec)
UB: Average urban benzene conc (μg/m³)
Considering the observed exposure levels, no acute effects from exposure to benzene are expected. The interest is focused on the prolonged chronic exposure which is responsible for leukemia. The estimated risk due to benzene exposure in the area under study is calculated considering:

- Benzene exposure levels
- Benzene internal concentration
- Biologically effective dose of benzene metabolites in target tissue (bone marrow)
- Dose response relationship
- Susceptibility of the population considering that the enzymes (CYP2E1, quinone reductase NQO1, and myeloperoxidase) related to benzene metabolism are polymorphic
- Benzene exposure during the day is not constant. Internal dose variation is exposure-dependent but not linearly linked to encountered microenvironment concentrations. Inhaled benzene and the produced metabolites are dynamically and continuously calculated through time (not just steady state estimations).
Advantages of Biology Based Exposure Assessment – mechanistic approaches

- Dose response relation takes into account the internal dose at the target tissue, which is the real exposure metric

- Multiple pathways (air, water, food, consumer products) and routes of exposure (inhalation, oral) for the same pollutant can be incorporated into the PBTK/D model and provide a realistic aggregate exposure assessment

- Biology-based dose response is more representative for low exposure levels, since epidemiological approaches are based on extrapolations obtained by incidences that occurred at exposure levels 4–5 orders higher

- Capturing both toxicokinetics, toxicodynamics and exposure dynamics allowed us to incorporate mechanistic knowledge on exposure assessment and thus improve on the validity and relevance of the dose-response relationship

- Traffic emissions and health endpoints are linked within a “continuous” mathematical frame allowing the exploration of alternative scenarios and the explicit incorporation of uncertainty and variability in the final risk estimates
Leukemia risk estimation

Distributions are necessary in order to describe:

- Variability in exposure
- Variability in enzymatic activity
Risk attributable to the activities

Activities contribution to the overall leukemia risk

- Smoking
- ETS
- Indoor loc. zone 3
- Indoor loc. Zone 2
- Indoor loc. Zone 1
- Driving
- Walking/outdoor
Traffic fleet composition under the “what if” scenarios

Fleet composition

<table>
<thead>
<tr>
<th>Current situation</th>
<th>1st Scenario</th>
<th>2nd Scenario</th>
<th>3rd Scenario</th>
<th>4th Scenario</th>
<th>5th Scenario</th>
<th>6th Scenario</th>
</tr>
</thead>
<tbody>
<tr>
<td>46%</td>
<td>20%</td>
<td></td>
<td>69%</td>
<td>40%</td>
<td></td>
<td>47%</td>
</tr>
</tbody>
</table>

Benzene emission reduction

<table>
<thead>
<tr>
<th>1st Scenario</th>
<th>2nd Scenario</th>
<th>3rd Scenario</th>
<th>4th Scenario</th>
<th>5th Scenario</th>
<th>6th Scenario</th>
</tr>
</thead>
<tbody>
<tr>
<td>46%</td>
<td>69%</td>
<td>47%</td>
<td>64%</td>
<td>77%</td>
<td>92%</td>
</tr>
</tbody>
</table>
Risk mitigation

Exposure Science Community of Practice Seminar, September 8, 2009

- Current situation
- Scenario 1&3
- Scenario 2
- Scenario 4
- Scenario 5
- Scenario 6

Amount of population (N/10^5)

Probability of cancer
Aggregate risk mitigation

Leukemia lifetime risk probability

Max
Min
Mean

a- current situation
b- theoretical scenario
c- expected scenario
d- optimal scenario
e- smoking ban

Non smokers | Smokers
---|---
a | b | c | d | e | c+e | a | b | c | d | e | c+e
Gasoline station effect

Measurements:
- benzene in 16 points around the gasoline station
- benzene urban background concentration
- benzene in a later point of the adjacent road (to optimize CALINE 4)
- traffic parameters of the adjacent road
- meteorological observations (wind, temp, humidity, cloudiness)
- fuel traded rate

\[ C_{\text{point}_i \_\text{gas.station}} = \left( C_{\text{point}_i \_\text{measured}} - C_{\text{background}} - C_{\text{point}_i \_\text{street}} \right) \]
Gasoline station effect

\[ C_B = \frac{F^{0.713} \cdot T^{0.0298}}{D^{0.95} \cdot W^{2.55}} \]
Exposure modelling by ANNs

See diagram for relative importance of factors influencing exposure.

- **INPUT** factors:
  - Amount of fuel
  - Wind speed
  - Temperature
  - Traffic flow
  - Urban background

- **HIDDEN** layer:

- **OUTPUT**:
  - Exposure

**Bar chart** showing relative importance:

- Car refuelling employees: 21.9%
- Employees of miscellaneous activities: 31.0%
- Cashiers: 27.8%

**Legend**:
- Background concentration
- Traffic flow
- Temperature
- Wind speed
- Amount of gasoline
Gasoline station effect

- General Population
- Gasoline Station Employees
- People living in the vicinity (North West side)
- People working in the vicinity (North East side)

Amount of population (N/10^5)

Probability of cancer
Health impact assessment of policies: the case of Arsenic
<table>
<thead>
<tr>
<th>Sector</th>
<th>Specific policies considered</th>
</tr>
</thead>
</table>
| Large combustion plants| Baseline 2010: IPPC Directive – BREF on large combustion plants  
                          Large Combustion Plants Dir (2001)  
                          Baseline 2020: Emerging techniques  
                          Directive 2001/77/EC – IGCC & supercritical polyvalent processes                                                                                   |
                          Baseline 2020 – emerging techniques in sintering, catalytic oxidation  
                          MFTR 2020 – new iron-making techniques: direct reduction/smelting reduction                                                                       |
| Cement industry        | Baseline 2010: IPPC Directive – BREF on cement and lime manufacturing  
                          Baseline 2020: FGD techniques, activated C filters for HM reduction  
                          MFTR 2010 = Baseline 2020  
                          MFTR 2020 = all plants with HM reduction technologies                                                                                               |
| Petrol                 | Baseline 2010: Directives 98/70/EC and 2003/17/EC  
                          - Ban in use of leaded petrol  
                          - 5 mg Pb/l in unleaded petrol  
                          - high % of passenger vehicles comply with Euro 2000 and 2005 norms  
                          - high % of HDV comply with Euro III norm  
                          Baseline 2020: significant % of LPG cars and lot of HDV comply with Euro IV and V  
                          MFTR 2010 = Baseline 2020 + increase of % of LPG cars  
                          MFTR 2020: increase of share of electric/FC cars                                                   |
Integrated risk assessment based on BED

- Environmental Modeling
  - Multi-route Transport, Transformation, and Accumulation

- Microenvironmental Modeling

- Potential Exposure

- Human Population Modeling
  - Population Distribution and Human Activity Patterns

- Physiologically Based Pharmacokinetic (PBPK) Modeling
  - Total Internal Dose and Target Tissue Dose

- Concentration Response

- Pharmacodynamic Modeling
  - Physiological Response
Modeling framework

- Stuttgart Emission Tool (SET) for country-specific emissions, by activity sectors
- MSCE-HM for transboundary transport across Europe
- WATSON for soil, water concentration and food-relevant exposure
- XtraFood for food contamination through plant uptake
- JRC BBDR platform and ISE for internal dosimetry and risk assessment
- VSL and contingent valuation functions for monetary cost assessment
- Quantification/reduction of uncertainty with MCMC
Spatial distribution of anthropogenic air emissions of arsenic in Europe for the year 2000 [kg/km²/y].
Spatial distribution of anthropogenic air emissions of arsenic in Europe (a) for the BAU scenario and (b) for the MFTR scenario projection of the year 2020 [t/y].
Spatial distribution of concentrations in European top-soils including adjacent territories [mg/kg] (a) and mean annual concentration in ambient air (b) for arsenic for the year 2000.
Spatial distribution of arsenic annual wet (a) and dry (b) deposition over Europe in 2000.
Contaminant flows in the food chain
Human exposure routes via contaminated food

- Pesticides
- Fertilizers, soil improvers
- Soil
- Air

Crop

Vegetables, cereals

Vegetable feed

Meat, milk, eggs

Cattle and poultry

Feed

Standard

Preparation

Standard

Preparation

Human diet

Exposure

Air, drinking water, ...

ADI, ARID, CSF

Dose-response; health impact valuation

Exposure and risk assessment, valuation of impact
As PBPK/PD model
Number of deaths due to lung cancer on country basis

- **AT**: 1, **BE**: 2, **BG**: 1, **CH**: 0, **CY**: 0, **CZ**: 1, **DE**: 8, **DK**: 2, **EE**: 1, **ES**: 4, **FI**: 1, **FR**: 5, **GR**: 1, **HU**: 1

Legend:
- **Base scenario (2000)**
- **BAU scenario (2010)**
- **MFTR scenario (2010)**
Number of deaths due to lung cancer on country basis
Lifetime exposure including:

- In utero exposure
- Newborn exposure
- Childhood exposure
- Adulthood exposure
Mother-fetus model for 2-generation effects
In utero exposure to dioxins

![Graphs showing concentration of TCDD in various blood samples over time.](image-url)
The case of Bisphenol A (BPA)
EFSA Tolerable Daily Intake (50 μg/kg BW/day)

Plasma concentration (μg/l)

Newborn  | 1 month  | 3 months  | 6 months  | 9 months  | 12 months  | 18 months  | 24 months
---|---|---|---|---|---|---|---
Dose: 0.25-0.4 μg/kg BW/day
Dose: 0.25-11 μg/kg BW/day
Dose: 2-13 μg/kg BW/day
Bisphenol A (BPA)

Gestation period (9 months)
Breast feeding (till 3rd month)
Bottle feeding from 6th to 9th month (7.5 μg/kg BW/d)
Bottle feeding from 9th to 18th month (13 μg/kg BW/d)
Bottle feeding from 18th to 24th month (5.3 μg/kg BW/d)
Benefits to public health – improved risk assessment

- Expressomics allowed identification of gene expression profiles characterising exposure to chemicals alone and in co-exposure to other substances.
- Gene expression profiles can be used as biomarkers of exposure taking into account risk modifiers such as:
  - diet
  - gender
  - age
  - time length of exposure
- Whole genome micro-arrays allow reviewing all gene associations modulating physiological response and identifying end points specific to the most significant associations.
- Bioinformatic data analysis holds great potential for building plausible mechanistic hypothesis on mechanism of action and exposure biomarker discovery.
Towards the exposome:

The exposome approach can be implemented coupling:
- macro-/micro-environmental modeling
- passive/active personal monitoring
- human biomonitoring
- expression biomarkers
- physiologically-based biokinetic modeling
- systems biology modeling

A tiered approach should be developed to use exposure information for toxicity prioritization:

**Tier 1**
- exposure surrogates
- sentinels of exposure

**Tier 2**
- Full chain exposure assessment
Thank you for your attention
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