Placental transfer to the foetus of xenobiotics (including pesticides)

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University of Bristol & United Bristol Healthcare NHS Trust
Fetal health risks

- Maternal exposure to environmental contaminants
- Placental transfer
- Fetal exposure – enhanced sensitivity: risk?
  - Radiation – dose: carcinogenicity
  - Pesticides – toxicity: allergy and carcinogenicity,
- European Environment & Health Strategy: SCALE initiative
  - Science, Children, Awareness raising, Legal instruments, Evaluation
- Long-term effects in adult life?
EU FPV Key action 4 –
Children’s Health and the
Environment
Placental Uptake and Transfer
of Environmental Chemicals
Relating to Allergy in
Childhood Years

a). Placental transfer
and biodistribution of
radionuclides
b). Biodistribution of
radionuclides from
chronic ingestion

(Health protection Division)
Plutocracy

Dr M Saunders, Bristol University, UK – Lead centre - placental transfer

IPCM, Bratislava, Slovak Republic – clinical data
Comenius University, Bratislava, Slovak Republic – clinical data

UMF, Bucharest, Romania – clinical data
Nat. R&D Inst. Env. Prot., Bucharest, Romania – Environmental sampling

VITO, Mol, Belgium - assays
UA, Belgium – clinical data

CDC/Emory University, Atlanta, USA - epidemiology
Placental transfer and fetal biodistribution

- Placental transfer of xenobiotics key element of hypothesis
- Experimental models allow control of exposure and analysis of transfer
- Fetal biodistribution will determine exposure levels of individual organs (mechanisms)
- Increased sensitivity during development
- Implications for function and outcome
Plutocracy - questions

• Unborn child more sensitive to environmental exposure effects
• Mechanisms, effects, long-term health outcomes
• Determine whether there is a link between *in utero* fetal exposure to environmental chemical pollutants (xenobiotics) and adverse outcomes
• Identification of risk factors
• Carcinogens, neurotoxicants…..
Plutocracy hypothesis

• Not genetics alone – environmental factors
• Maternal exposure to environmental chemicals (xenobiotics) occurs during pregnancy
• Placental transfer may lead to fetal exposure
• Skewing of in utero Th1/Th2 cytokine balance – inappropriate bias towards allergic profile and away from cell surveillance
Objectives

• Recruitment of 200 pregnant women @ 5 regions of differing environmental characteristics
• Analysis of atopic status (specific IgE) – wide variation
• Follow-up of 100 women and offspring per region
• Biological samples, exposure assessment, clinical evaluation of children
• Bristol’s contribution - Placental transfer
Measurements

- Biological samples: Peripheral blood, placenta, cord blood, breast milk
- Chemical analysis: inorganic XB (Pb, Cd) using AAS; organic XB using GCC – levels in different regions
- Risk factor assessment – questionnaires
  - Biographical data, newborn parameters, SES, household characteristics, environmental exposure (smoking, housing, heating, pets), allergic status
  - Prenatal and postnatal assessment
# Atopic incidence - mothers

<table>
<thead>
<tr>
<th>Area</th>
<th>% atopic</th>
<th>% non-atopic</th>
<th>other</th>
</tr>
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<tbody>
<tr>
<td>Bratislava</td>
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<td>38</td>
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<tr>
<td>St Lubovna</td>
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<td>Bucharest</td>
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<td>Giurgiu</td>
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<td>Mol</td>
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### List of selected persistent organochlorine compounds

<table>
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<tr>
<th>A</th>
<th>B</th>
<th>C</th>
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<tr>
<td>1,4+1,3-DCB</td>
<td>1,2-DCH</td>
<td>PCB - 28</td>
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<tr>
<td>1,2-DCB</td>
<td>1,2-DCH</td>
<td>PCB - 52</td>
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<tr>
<td>1,3,5-TCB</td>
<td>1,3,5-TCB</td>
<td>PCB - 101</td>
</tr>
<tr>
<td>1,2,4-TCB</td>
<td>1,2,4-TCB</td>
<td>PCB - 118</td>
</tr>
<tr>
<td>1,2,3-TCB</td>
<td>1,2,3-TCB</td>
<td>PCB - 138</td>
</tr>
<tr>
<td>TeCB</td>
<td>TeCB</td>
<td>PCB - 153</td>
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<tr>
<td>PCB</td>
<td>PCB</td>
<td>PCB - 180</td>
</tr>
<tr>
<td>HCB</td>
<td>PCB</td>
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</tr>
</tbody>
</table>

**Chemical names and abbreviations:**

- **1,2-dichlorobenzene (1,2-DCB)**
- **1,3,5-trichlorobenzene (1,3,5-TCB)**
- **1,2,4-trichlorobenzene (1,2,4-TCB)**
- **1,2,3-trichlorobenzene (1,2,3-TCB)**
- **Tetrachlorobenzene (TeCB)**
- **Sigma (Σ) 1,2,3,5+1,2,4,5-tetrachlorobenzene (Σ 1,2,3,5+1,2,4,5-teCB)**
- **Pentachlorobenzene (PCB)**
- **Hexachlorobenzene (HCB)**
- **Alpha-hexachlorocyclohexane (alpha-HCH)**
- **Beta-hexachlorocyclohexane (beta-HCH)**
- **Gamma-hexachlorocyclohexane (gamma-HCH)**
- **Delta-hexachlorocyclohexane (delta-HCH)**
- **1,1,1-trichloro-2,2-bis(p-chlorophenyl)ethane (p,p'-DDT)**
- **1',1'-dichloro-2,2-bis(p-chlorophenyl)ethylene (p,p'-DDE)**
- **2,4,4'-trichlorobiphenyl (PCB - 28)**
- **2,2',5,5'-tetrachlorobiphenyl (PCB - 52)**
- **2,2',4,5,5'-pentachlorobiphenyl (PCB - 101)**
- **2,3',4,4',5-pentachlorobiphenyl (PCB - 118)**
- **2,2',3,4,4',5'-hexachlorobiphenyl (PCB - 138)**
- **2,2',4,4',5,5'-hexachlorobiphenyl (PCB - 153)**
- **2,2',3,4,4',5,5'-heptachlorobiphenyl (PCB - 180)**

**Additional notes:**

- **14C-labelled version available**

**Abbreviations:**

- **A** - chlorinated benzenes
- **B** - organochlorine insecticides
- **C** - polychlorinated biphenyls (indicator congeners)
Radionuclides

• Environmental exposure to ionising radiation
  – global fallout from weapons testing
  – marine discharges
  – reactor accidents e.g. Windscale, Three Mile Island
• Heightened interest after Chernobyl (1986)
• *In utero* exposure of particular concern
• Increased risk of death, growth disorders, malformations, functional impairment and carcinogenesis
• Higher incidence of childhood thyroid cancer (and infant leukaemia?) rates after Chernobyl
Objectives

• Measure placental transfer of environmental radio-nuclides to which women may be exposed during pregnancy e.g. iodine, strontium

• Compare exposure duration, route of administration *in vivo* and gestational stage

• Compare maternal and fetal biodistribution

• Estimate fetal radiation dose from environmental exposure in pregnancy
Estimates of dose

- Greater than predicted medical effects from Chernobyl e.g. increased incidence of childhood thyroid cancer
- Past assumption that dose to fetus would be equivalent to that received by uterus
- Fails to include component resulting from placental transfer and fetal organ uptake
- May result in an underestimation of fetal dose
Radionuclides

- Pertechnetate Tc-99m
- Iodine I-131
- Calcium Ca-45
- Strontium Sr-85
- Iron Fe-59
- Cobalt Co-57
Models

• Human *in vitro* perfused placenta
• *In vivo* animal model for biodistribution by following tracer levels

• Combine with exposure information from selected subjects to determine likely fetal organ exposure (Plutocracy)
Ex-vivo perfused human placenta
Ex-vivo perfused human placenta

- Elective section – no adverse pathology
- Collection within 10 minutes of delivery
- Fetal pressure <40mm Hg
- Fluid loss < 3.33% (flow rate 6ml/min)
- Temp 37°C (± 0.5), pH 7.4 (± 0.1)
- Constant glucose consumption and lactate production
- Adequate transfer and equilibrium levels of perfusion marker – antipyrine
Perfused placenta - method

- Fresh placenta obtained from Caesarean delivery without adverse pathology
- Medium 199 supplemented with Heparin, Dextran, BSA and sodium bicarbonate
- Placenta maintained at 37°C, pH 7.4 and fetal and maternal sides cannulated and perfused with supplemented medium, 50% O₂, 45% N₂, 5% CO₂
- $^{14}$C-POP - 10µCi (0.37MBq)
- Labelled compound added to maternal side and samples removed from maternal and fetal circulation at time intervals up to 120 minutes
Placental transfer of I-131 in vitro

Time (mins) | % transfer
---|---
0  | 100
20 | 80
40 | 60
60 | 40
80 | 20
100| 0
120| 0

Maternal vs. Fetal

% transfer vs. Time (mins)
Transfer of environmental radionuclides across the human *in vitro* perfused placenta

Time after administration

% administered activity

Fetal uptake

- I-131
- Ca-45
- Sr-85
- Co-57
- Fe-59
Technical problem
• Recirculating system
• Equilibrium apparently reached after about 30 mins
• False/premature equilibrium caused by excessive loss of DCB from system, particularly on the maternal side.

Solution
• Silicone tubing replaced by Flourel
• Pre-gassing – direct oxygenation of perfusate avoided
• Extra albumin added (+0.4%, total 1.1%)
• Rapid transfer and nature of DCB (recirc. losses) – more suited to open circuit design
Placental perfusion open circuit schematic

- Pressure gauge
- Bubble trap
- “Fetal artery”
- “Fetal vein”
- Maternal venous sampling site
- Fraction collector
- O2 probe
- Pump
- Heat exchanger 37°C
- Maternal arterial sampling site
- Maternal venous sampling site
- Maternal artery reservoir
- Fetal artery reservoir
- Stirrer
- Venous waste
- 95% O2, 5% CO2
- 95% O2, 5% CO2
Open circuit system

- Non-recirculating
- Clearance:
  \[ Cl = \left( \frac{\text{Recipient vein conc}}{\text{Donor art. conc}} \right) \times \text{recipient flow rate (ml/min)} \]
  - the greater the value, the greater the transfer
- Clearance index:
  \[ Cl_I = \frac{Cl \text{ (test compound)}}{Cl \text{ (ref. compound)}} \]
  expressed as ratio
Open circuit - solutions

- Much reduced loss of DCB
- No recirculation (~7x in CC)
- Positive displacement
  - Constant Ma concentration
  - Less contact with tubing
  - Enclosed – pH maintained/ air exposure reduced
  - Ma taken just before entry into placenta
- Extra albumin (total 1.1%) as before
Open circuit - M to F, representative clearance values

- **DCB**: Red line
- **Antipyrine**: Pink line
- **Creatinine**: Green line

**Clearance (ml/min)**

**Time (mins)**: 0 5 10 15 20 25 30

- 1.1% BSA Medium to 0.7% BSA on F side
Mean Clearance indices for DCB (n = 5), MOC to FOC, with s.e.m.

![Graph showing Mean Clearance indices for DCB (n = 5), MOC to FOC, with s.e.m.](image_url)
CI₁ (DCB/antipyrine) the best measurement

- Overcomes much experimental variation
- Most consistent measurement between expt
- DCB and antipyrine very similar in behaviour
- Other organochlorines expected to behave as antipyrine
Mean Clearances, MOC to FOC, with sem.

Clearance ml min$^{-1}$

time (mins)

DCB, n=5
DDT, n=10
DDE, n=8
PCB-77, n=6
### Table 1a  Placental transfer of pesticides ex-vivo

<table>
<thead>
<tr>
<th>Pesticide</th>
<th>Maternal to fetal transfer</th>
<th>Fetal to maternal transfer</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean clearance index (s.e.m.)</td>
<td>Mean clearance index (s.e.m.)</td>
</tr>
<tr>
<td>DCB</td>
<td>0.98 (0.02)</td>
<td>0.92 (0.03)</td>
</tr>
<tr>
<td>DDT</td>
<td>0.61 (0.01)</td>
<td>0.61 (0.01)</td>
</tr>
<tr>
<td>DDE</td>
<td>0.61 (0.01)</td>
<td>0.59 (0.03)</td>
</tr>
<tr>
<td>PCB-77</td>
<td>0.73 (0.02)</td>
<td>0.73 (0.03)</td>
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</tbody>
</table>

### Table 1b  Accumulation in perfused area of placenta ex-vivo

<table>
<thead>
<tr>
<th>Pesticide</th>
<th>Maternal to fetal transfer</th>
<th>Fetal to maternal transfer</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean % uptake (s.e.m.)</td>
<td>Mean % uptake (s.e.m.)</td>
</tr>
<tr>
<td>DCB</td>
<td>4.2 (0.6)</td>
<td>3.7 (0.7)</td>
</tr>
<tr>
<td>DDT</td>
<td>23.4 (2.2)</td>
<td>20.2 (0.9)</td>
</tr>
<tr>
<td>DDE</td>
<td>18.0 (1.5)</td>
<td>18.9 (1.6)</td>
</tr>
<tr>
<td>PCB-77</td>
<td>22.5 (1.3)</td>
<td>22.3 (2.1)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Pesticide</th>
<th>Maternal to fetal transfer</th>
<th>Fetal to maternal transfer</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean % uptake/g (s.e.m.)</td>
<td>Mean % uptake/g (s.e.m.)</td>
</tr>
<tr>
<td>DCB</td>
<td>0.18 (0.01)</td>
<td>0.17 (0.01)</td>
</tr>
<tr>
<td>DDT</td>
<td>1.21 (0.11)</td>
<td>1.22 (0.08)</td>
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<tr>
<td>DDE</td>
<td>0.96 (0.14)</td>
<td>0.96 (0.14)</td>
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<tr>
<td>PCB-77</td>
<td>1.75 (0.15)</td>
<td>1.91 (0.27)</td>
</tr>
</tbody>
</table>
Ex vivo pesticide results summary

- No significant difference between DDT and DDE transfer
- Highly significant differences between all other compounds
- DCB > PCB-77 > DDE > DDT extent of transfer
- M-F similar to F-M – no backflow
- Passive diffusion in both directions
- Significant accumulation of DDT, DDE, PCB-77 but not DCB in placental tissue
Physical properties as a transfer/accumulation predictor

• Transfer and accumulation of xenobiotics seems to be related to their physical properties.
• The partition coefficient between octanol and water, $P_{o/w}$, determines lipophilicity.
• The compounds used here segregate similarly in terms of $P_{o/w}$ (MW) and placental transfer.
• $P_{o/w}$ and MW seem to be a good general predictors of transfer/accumulation in these experiments.
In vivo uptake and biodistribution
Experimental design: Pesticides

- Pregnant guinea pig
- 1h....72h
- (7 time-points)
- Sacrifice by anaesthetic overdose
- Dissect organs
- Count samples & standards
- Process data

0.37 MBq (10uCi) in 0.25ml corn oil

$^{14}$C-POP (x5)
Comparison of pesticide levels in selected tissues

Adult blood

Fetal blood

Amniotic fluid

Placenta

Comparison of pesticide levels in selected tissues

% administered activity

Time after administration (h)
Maternal-fetal biodistribution in late gestation - DCB
Maternal-fetal biodistribution in late gestation - DDE

Blood

Skin

Liver

Fat

% activity/g tissue

Time after administration (h)

Maternal
Fetal
Maternal-fetal biodistribution in late gestation - PCB-52

Blood

Skin

Liver

Fat

Time after administration (h)
Maternal-fetal biodistribution in late gestation - DCB

- **Blood**
- **Spleen**
- **B-marrow**
- **Thyroid (I-131)**

% adm. activity/g tissue vs. Time after administration (h)

Legend:
- Red square: Maternal
- Blue triangle: Fetal
In vivo results - pesticides

- Rapid transfer across the placenta - all compounds
- Peak fetal uptake at 6 hours
- Fetal concentrations can exceed maternal levels:
  Blood (plasma and erythrocytes), Spleen, Muscle, Femur, Brain, Bone marrow, Liver, Fat
- Implications for development due to increased sensitivity of fetus?
- Exact levels unknown but implications for carcinogenesis, neurotoxicity etc.
- Spin-off study approved for funding: in vitro immune function
Conclusions

- Concordance between models
- Rapid placental transfer
- Fetal organ uptake
- Different pattern of biodistribution
- Potential detriment: immunological, neurological and hepatic function
- Useful base for interpretation of clinical findings
- More information needed re. *in utero* exposure
Discussion

• Useful screening technique applicable to a range of compounds
• Drawbacks – technically challenging, availability, isolated organ, perfusate/carrier effects
• Integration with data from other models
Policy implications - 1

• Options: removal, reduction, mitigation of exposure
• Ban on usage is gradually reducing levels in the population but OCs do bioaccumulate
• Not all countries have imposed a complete ban e.g. developing countries: DDT – crops, mosquito control
• Even where banned, detectable levels in blood, breast milk (but reducing with time e.g. DDT, DDE in breast milk and fat
Policy implications - 2

• Reduction of harm from exposure
• Remediation of soil, alternate supplies of food sources; alternative pesticides?
• Requires more knowledge – distribution and effects – is there a risk at current exposure levels and what are they?
  – Standardisation of methodology, removal of bias, regional variation, increase number and size of studies
Policy implications - 2

• Peak exposure: 1960’s – fetal origins of adult disease?
• Healthy eating – conflicting advice
  – food groups during pregnancy e.g. salmon, selected vegetables
• Uncertainty amongst the public e.g. recent salmon scare – what is safe?
Policy implications - 4

• The fetus/neonate/infant is not just a small adult – appropriate PK models and dosimetry
• Route of exposure: fetus, neonate, infant
• Databases, birth cohorts, biobanks, biomonitoring, outcome measures, biomarkers
• Intervention – block fetal transfer – new models to test
• Imports from other countries
• Combined exposure effects
• European-wide cooperation and legislation
Radionuclides – oral gavage (new study)

1h….3 wks
(10 time-points)

Sacrifice by anaesthetic overdose

Pregnant guinea pig (mid and late gestation)

Dissect organs
Count samples & standards
Process data

1 - 4 MBq
I-131

0.3 – 1.2 MBq
Sr-85

0.25ml oral bolus in water
Radioisotopes-biodistribution

**Acute – single dose**
- Cardiac injection under anaesthesia
- 0.5 - 96 hours
- Sacrifice by anaesthetic overdose
- Dissect organs
- Count samples & standards
- Process data

**Chronic**
- Administered in drinking water
- Dosed daily for maximum of 21 days
- Sacrifice by anaesthetic overdose
I-131 bolus - Fetal biodistribution (early pregnancy)

Time after injection (h)

% I.A./g

Amniotic
Placenta
Body

Time after injection (h)
Biodistribution of I-131 in late pregnancy (i.c. injection)

- Blood
- Liver
- Spleen
- B-marrow
- Thyroid
- Thymus

% I.A./g vs. Time after injection (h)

- Maternal: Red
- Fetal: Blue
Biodistribution of I-131 at time of peak total fetal uptake (4h) following bolus administration in late gestation
Biodistribution of Sr-85 at time of peak total fetal uptake (24h) following bolus administration in late gestation
Biodistribution of Ca-45 at time of peak total fetal uptake (24h) following bolus administration in late gestation.
Biodistribution of Fe-59 at time of peak total fetal uptake (72h) following bolus administration in late gestation.
% total fetal uptake
(late gestation – bolus)

<table>
<thead>
<tr>
<th>Radionuclide</th>
<th>% max uptake</th>
<th>Time (h)</th>
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<td>Ca-45</td>
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<td>Sr-85</td>
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<td>I-131</td>
<td>10.9</td>
<td>72</td>
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<td>Fe-59</td>
<td>10.8</td>
<td>4</td>
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<td>Tc-99m</td>
<td>4.6</td>
<td>4</td>
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<td>Co-57</td>
<td>4.1</td>
<td>24</td>
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</table>
Comparison of *in vitro* and *in vivo* transfer across the placenta

<table>
<thead>
<tr>
<th>% transfer of radionuclides to fetal circulation (<em>in vitro</em>) or to whole fetus (<em>in vivo</em>)</th>
<th>In vitro perfused placenta</th>
<th>Acute <em>in vivo</em> administration</th>
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<tbody>
<tr>
<td></td>
<td>I-131</td>
<td>26.3</td>
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<td>Ca-45</td>
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<td>Co-57</td>
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<td>Peak uptake</td>
<td>24h</td>
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<td>Lungs</td>
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<td>Thymus</td>
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<td>0.3</td>
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<td>Carcase</td>
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<td>5.6</td>
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<td>Gestn stage</td>
<td>Stage 2</td>
<td>Stage 3</td>
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<tr>
<td>RBC</td>
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<tr>
<td>Plasma</td>
<td>0.6</td>
<td>0.4</td>
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<tr>
<td>Heart</td>
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<td>0.7</td>
</tr>
<tr>
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<tr>
<td>Tooth</td>
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</table>
Dosimetry calculations - I

- Calculate area under time-activity curve for each organ using exponential extrapolation beyond last time-point
- Divide total area by injected activity to get residence time
- Multiply residence time by dose per unit accumulated activity (or $S$ value) for each organ in turn
S-Value is scaled to body size for each isotope and depends on the organ volume and range of the radiation.

It is relatively simple to transfer data from small animals to human adult or foetus.
Dosimetry calculations - II

- Sum contributions from all organs, acting as sources, to the fetus acting as target including self-dose
- Calculations using MIRDOSE3 - phantoms for pregnant female at various stages of pregnancy provide appropriate S values
- Assume biodistribution and % transfer of radioactivity will be similar in human compared to guinea pig
Dosimetry calculations - III

• For fetal organ doses assume full term phantom in MIRDOSE3 appropriate
• Scale individual organ S-values by ratio of fetus to new-born total body S values
• Multiply organ residence times by scaled S-values to obtain organ doses
• Include maternal contribution from 9 month pregnant female phantom (whole fetus)
<table>
<thead>
<tr>
<th>Radionuclide</th>
<th>Gestational stage</th>
<th>Fetal dose (mGy/MBq)</th>
<th>Primary contributor</th>
<th>% contribution</th>
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Ca-45 fetal organ dosimetry

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Fe-59 fetal organ dosimetry

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Co-57 fetal organ dosimetry

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## I-131 fetal organ dosimetry

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<tr>
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Conclusions

• Unexpected preferential uptake in fetal organs
  – I-131: thyroid
  – Sr-85: bone marrow
  – Ca-45: bone marrow
• Acute and chronic exposures give different uptake levels with chronic generally > acute
• Results in higher fetal organ dose (but intake levels are lower for environmental agents)
• Suggests the risk for cancer induction in-utero is far higher than simple model calculations
• We should be able to have some conclusions about pesticides shortly – from the clinical data
Summary

- Simple in-vitro models are useful
- Some in-vivo work is essential
- The fetus is particularly at risk from selective uptake and retention
- Pesticide effects are NOT well understood
- The ex-vivo model can replace animals in research
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causal mechanisms
prevention