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alimentation, environnement, travail

Connaître, évaluer, protéger

Use of modelisation tools to assess risks related to cadmium exposure for workers and consumers

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Problem Formulation

Hazard | **Cd** | **Exposure**

- **Highly persistant environmental toxicant Bioaccumulable** -> elimination half-life : 10 to 30 years
- Accumulation in liver and kidneys
- **Acute Toxicity** («itaï-itaï» disease)
- **Chronic Toxicity**: repeated exposure→ kidney diseases, bone disease, reprotoxicity….
- Carcinogenic group 1 (IARC) and 1B (EU)

- Food as the most important source of exposure (excluding tobacco)
- Anses opinion from 2011 and 2016 following TDS2 and TDSi showing increased exposure to Cd and part of the population above the reference values: children (15%) and adults (0,6%)
- Recommendation to reduce exposure by limiting cadmium in the fertilizing materials

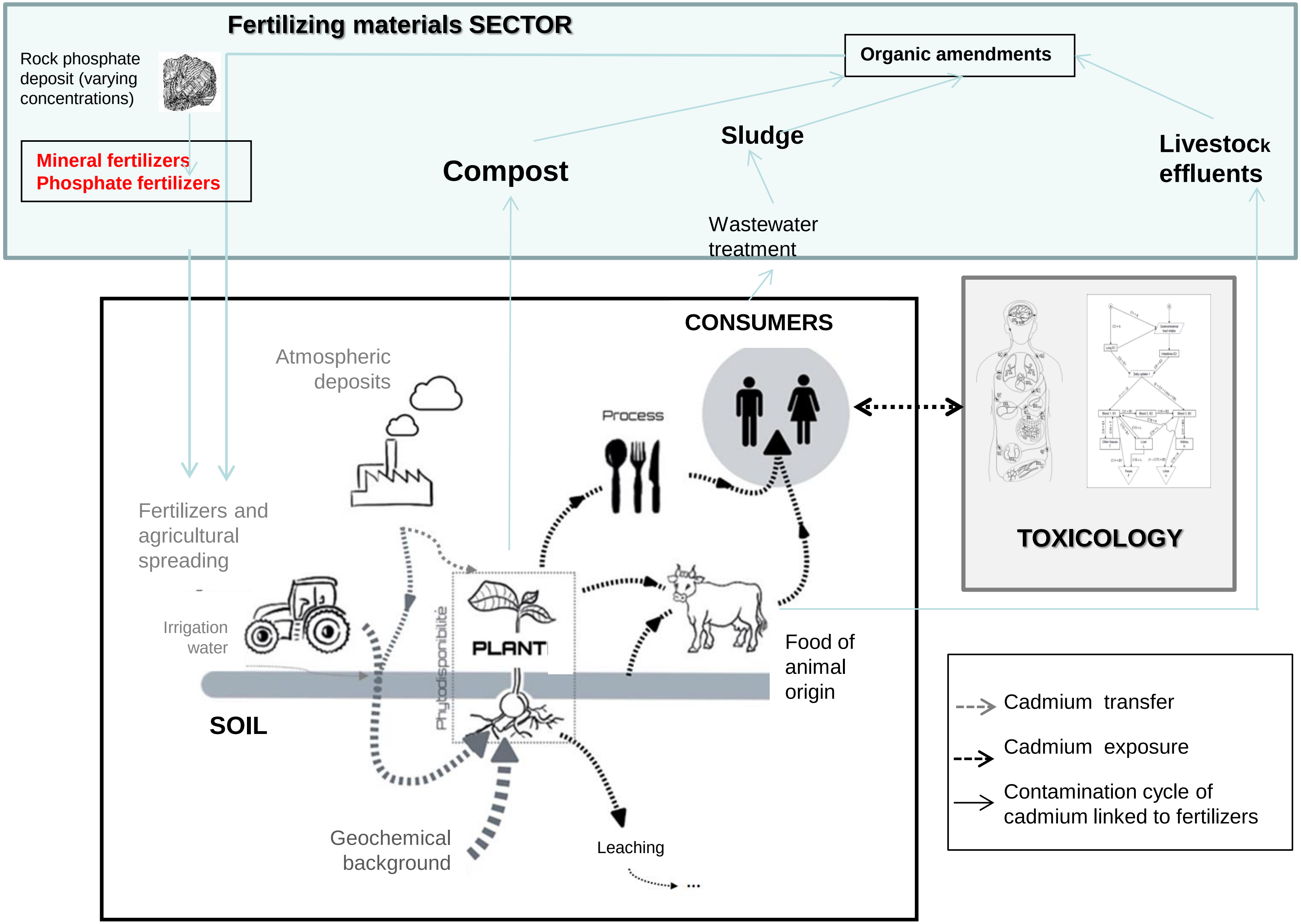
SCOPE

→ Update of the reference values (oral and internal values)

→ Market studies on fertilizing materials

→ **Proposals for limits values of cadmium** in fertilizing materials to reduce soil contamination and exposure

Conceptual Scheme



Hazard Characterization

Cadmium Toxicity

Target organs following repeated oral exposure: kidneys and bone tissues

JECFA, EFSA, ATSDR, ANSES

Kidney:

Accumulation of Cd in renal tissus (proximal tubes, renal cortex)

→Degenerescence and tubular atrophy

→release of low molecular weight proteins (β-2-microglobuline, retinol-binding protein (RBP), α-1-microglobuline,…)

Bone effects:

Decrease in bone density

Osteomalacia, Osteoporosis

Fractures

In women and men

Hazard Characterization

« Swedish Mammography Cohort » (sub cohort included)

2003-2009 ♀ living in Uppsala

Engström 2011
2688 ♀ (56-69 ans)
Relation between long-term exposure to Cd and bone effects
(osteoporosis + fractures)

Reference Population:
< 0.5 µg / g creat.

J Bone Miner Res. 2011, 26, 3, 486-495

Engström 2012
2676 ♀ (49-62 ans)
Association between Cd_{food} and bone density
Food questionnaire (1997) + [CdU] (2004-2008)
Osteoporosis and 1st fracture

Reference Population:
CdU<0.5 µg / g creatinine +
Cd_{al}<13 µg/d

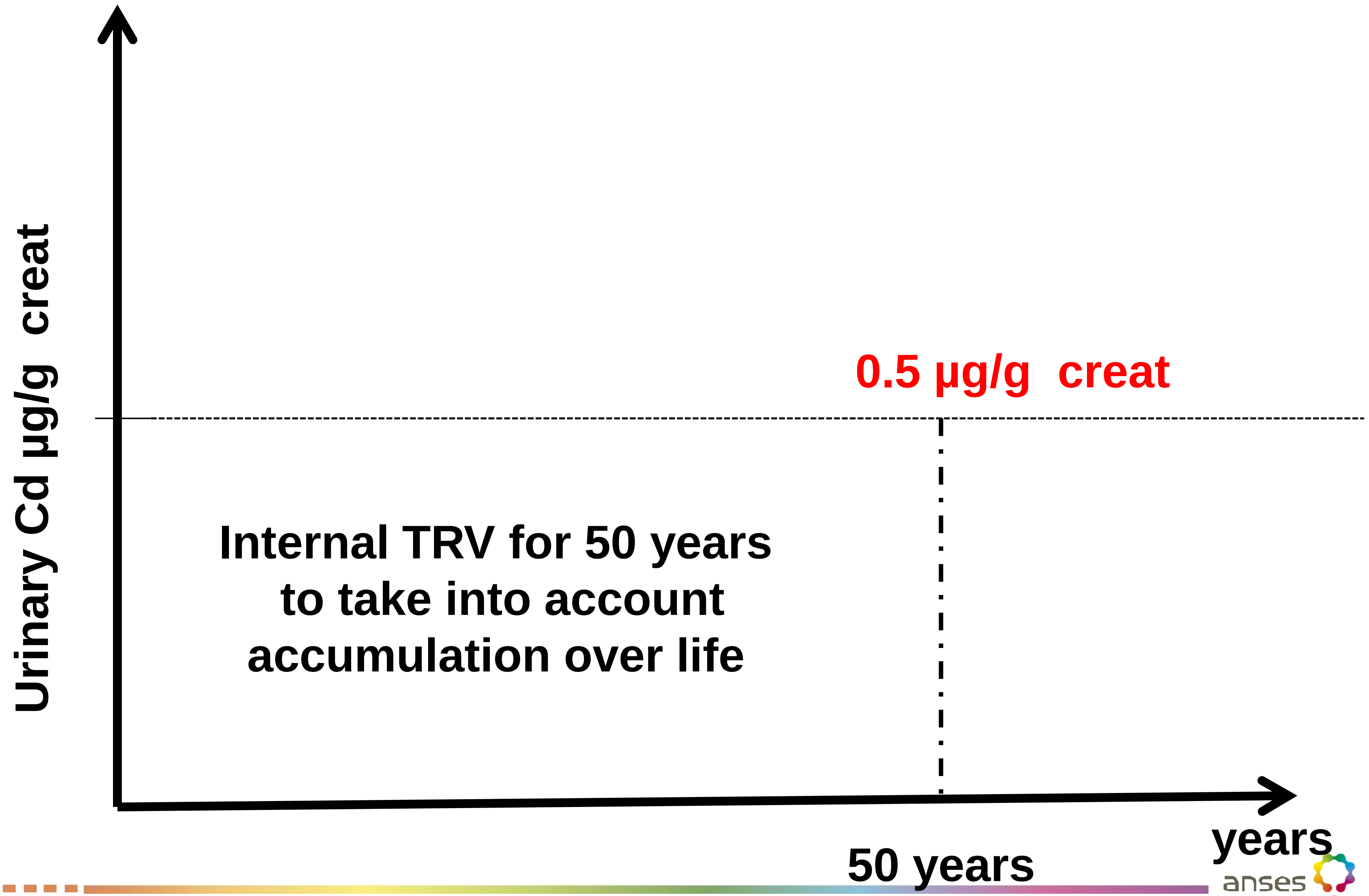
Bone 2012, 50, 1372-1378

Bone Effects (Engström 2011)

		ORs (95% IC)	
		∑ Women	Non-smokers
neck of femur	< 0.5 µg / g creat.	1.00 (réf)	1.00 (réf)
	0.5-0.75 µg / g creat	**2.17 (1.51-3.11)**	**2.09 (1.12-3.93)**
	>0.75 µg / g creat	**2.45 (1.51-3.97)**	**3.47 (1.46-8.23)**
Rachis	< 0.5 µg / g creat.	1.00 (ref)	1.00 (ref)
	0.5-0.75 µg / g creat	1.30 (0.91-1.86)	1.17 (0.64-2.15)
	>0.75 µg / g creat	**1.97 (1.24-3.14)**	**3.26 (1.44-7.38)**

Increased risk of osteoprosis and fractures after long term exposure to CdU> 0.5 µg / g créat)

Reference value



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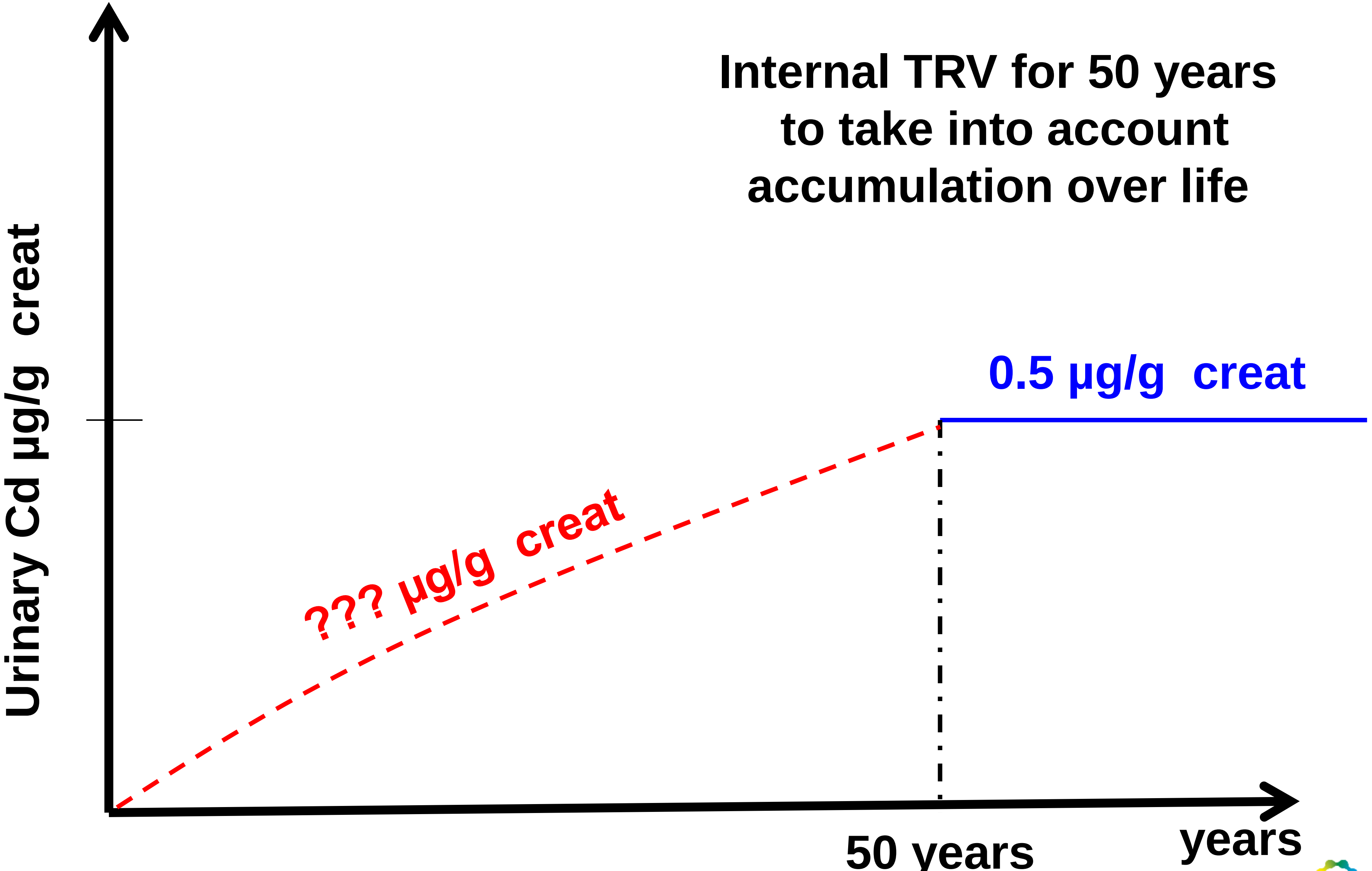
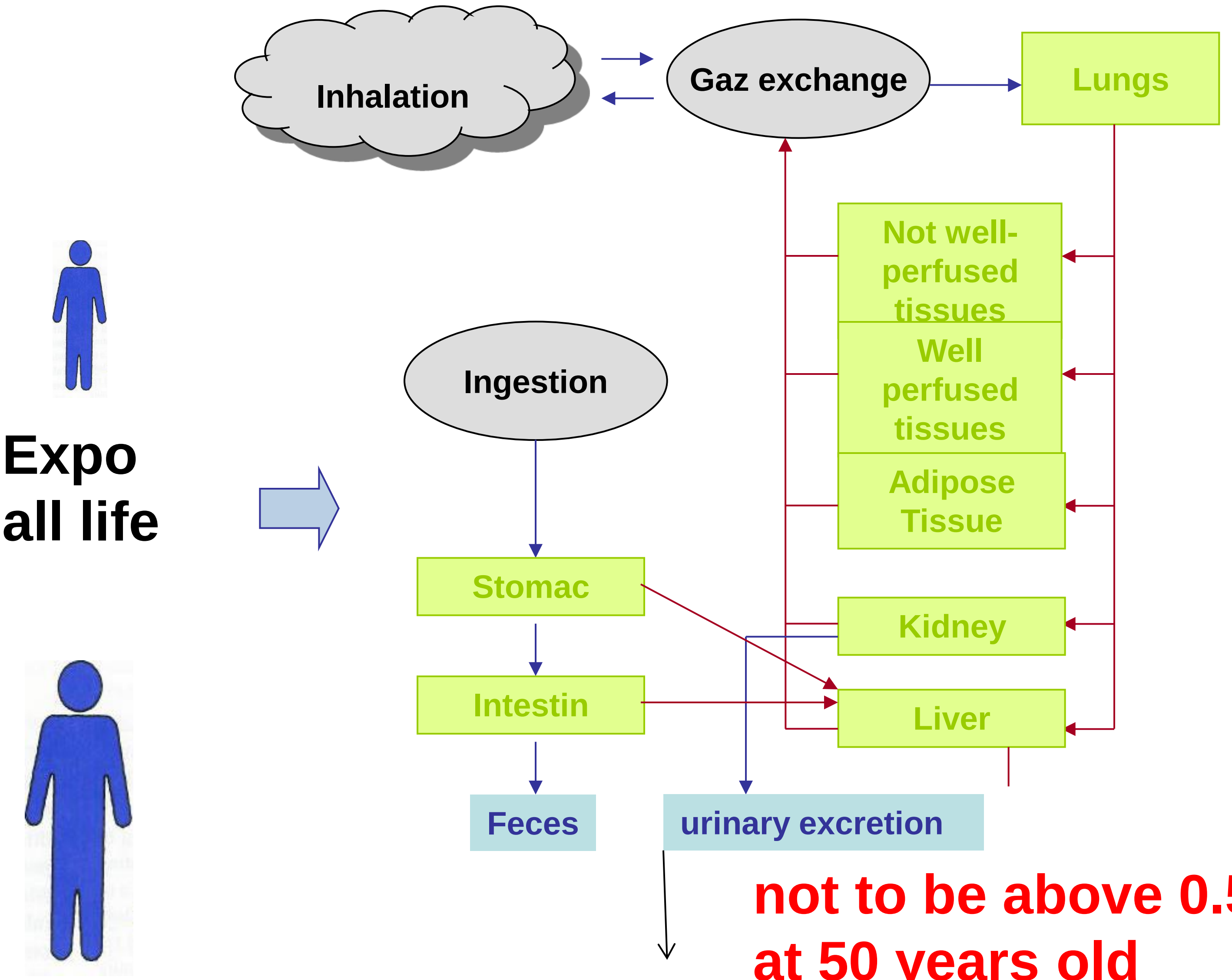
Reference value



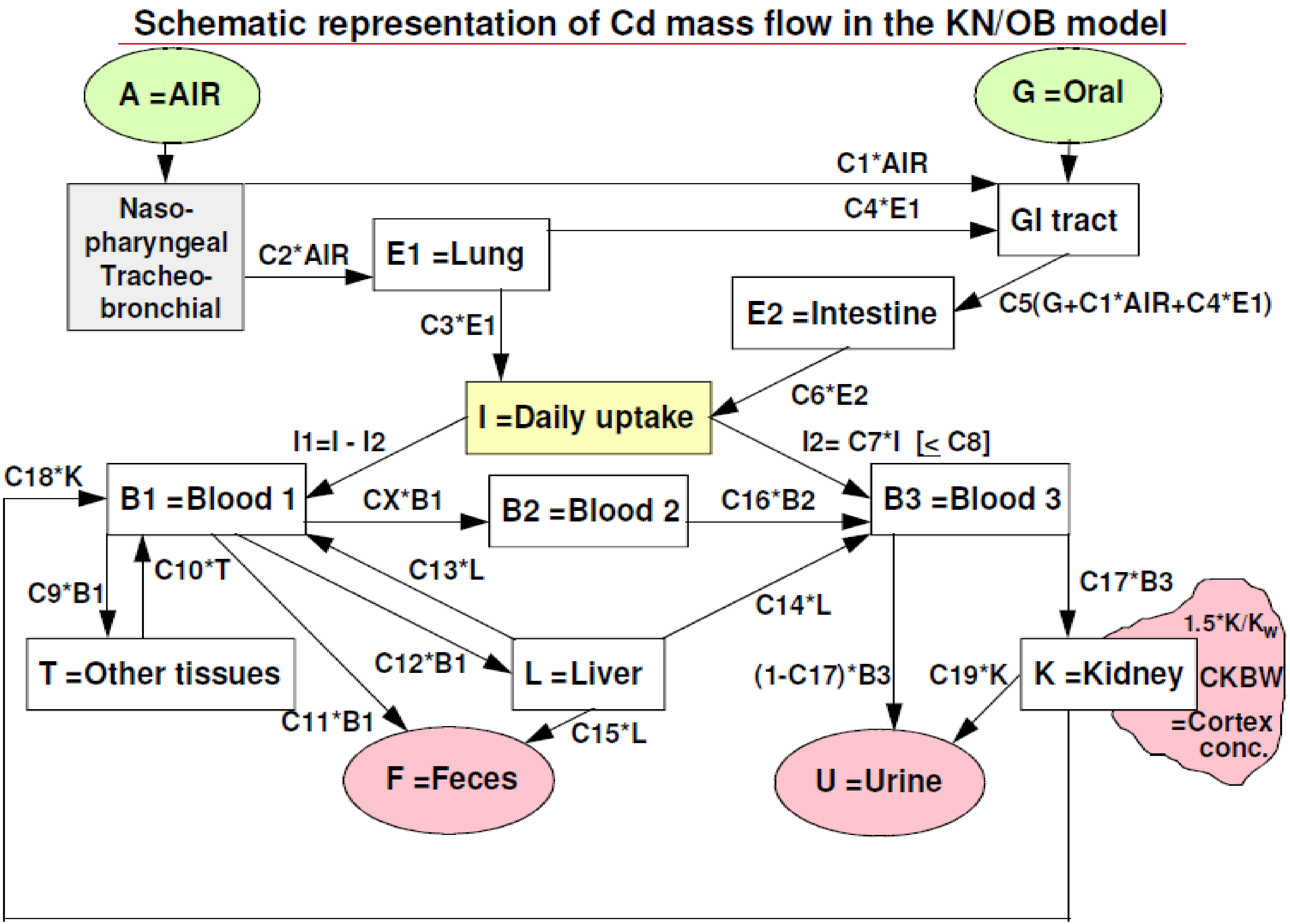
PBPK Model



Expo all life

not to be above 0.5 µg/g creat at 50 years old

models of Kjellström and Nordberg (1978)



Modelisation

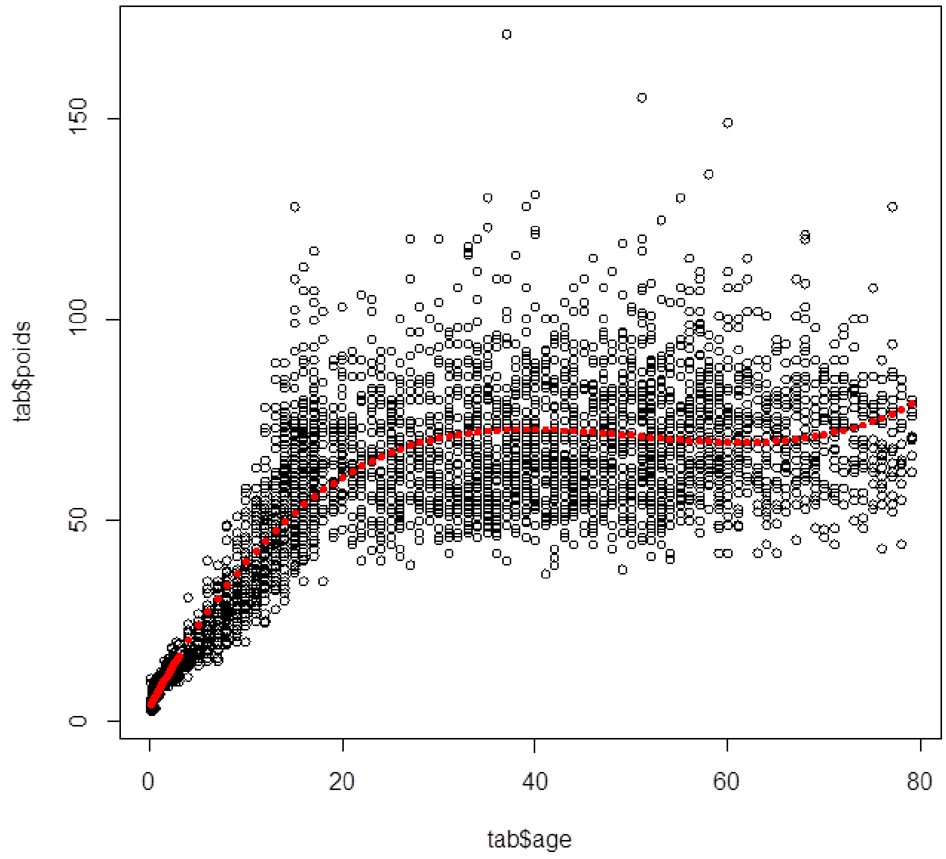
- Berkeley Madona tool

- PBPK model from Kjellström and Nordberg (1978)
Codes sent to Anses by ATSDR

- Specific Algorithm to take into account increased body weight depending on age: French data

Gault et Cockroft equation (not for children):
Cr 24h/day = (28—0.2 x age) x weight

Specific Algorithme to take into account increased body weight depending on ages: French data

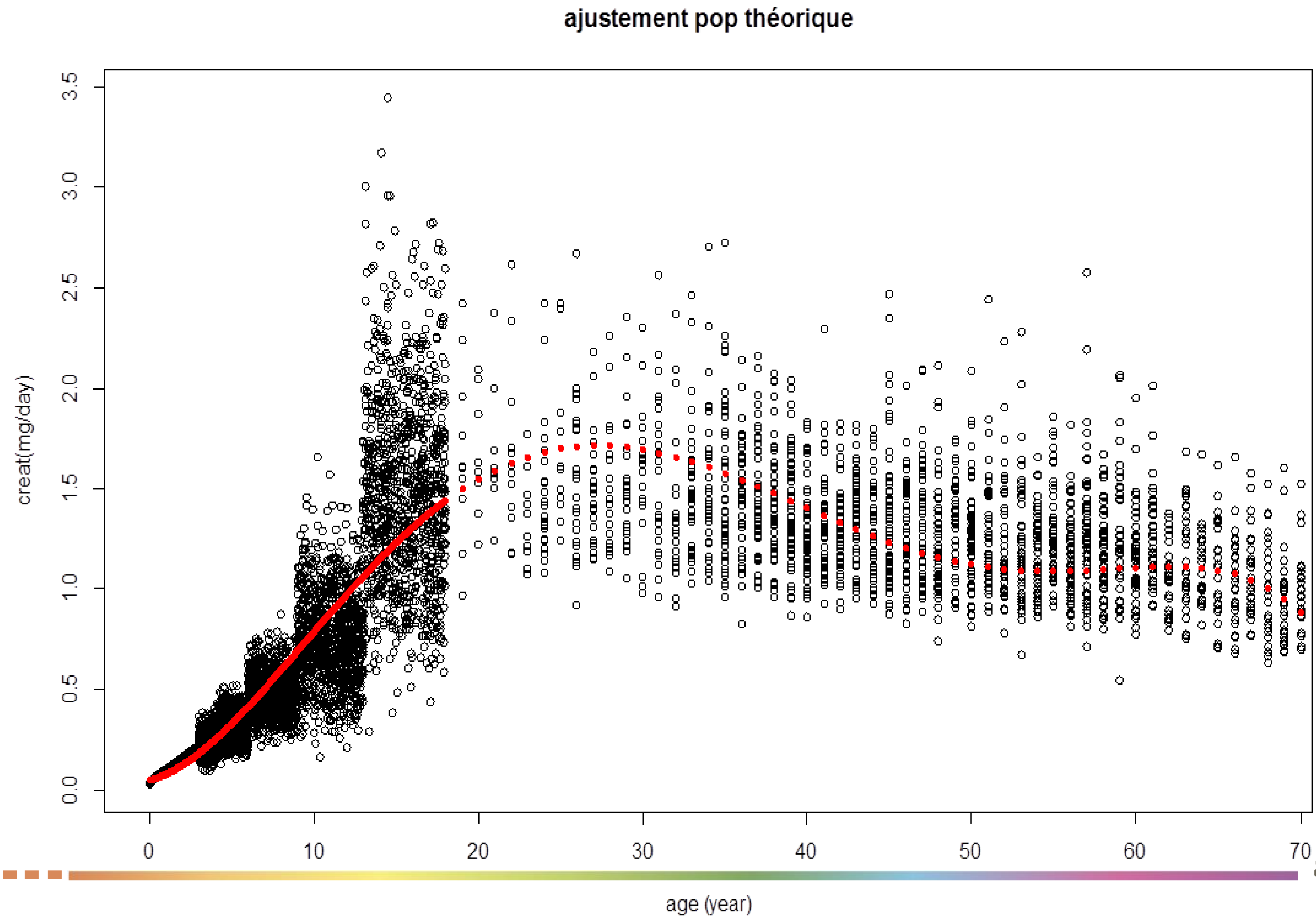


polynomiale regression based on TDS2 and TDSi

population 3 months to 79 years, n =4781

Weight = 3.68+4.47*age-0.093*age^2+0.00061*age^3

Algorithme for urinary excretion of creatinine: French data depending on body weight and ages

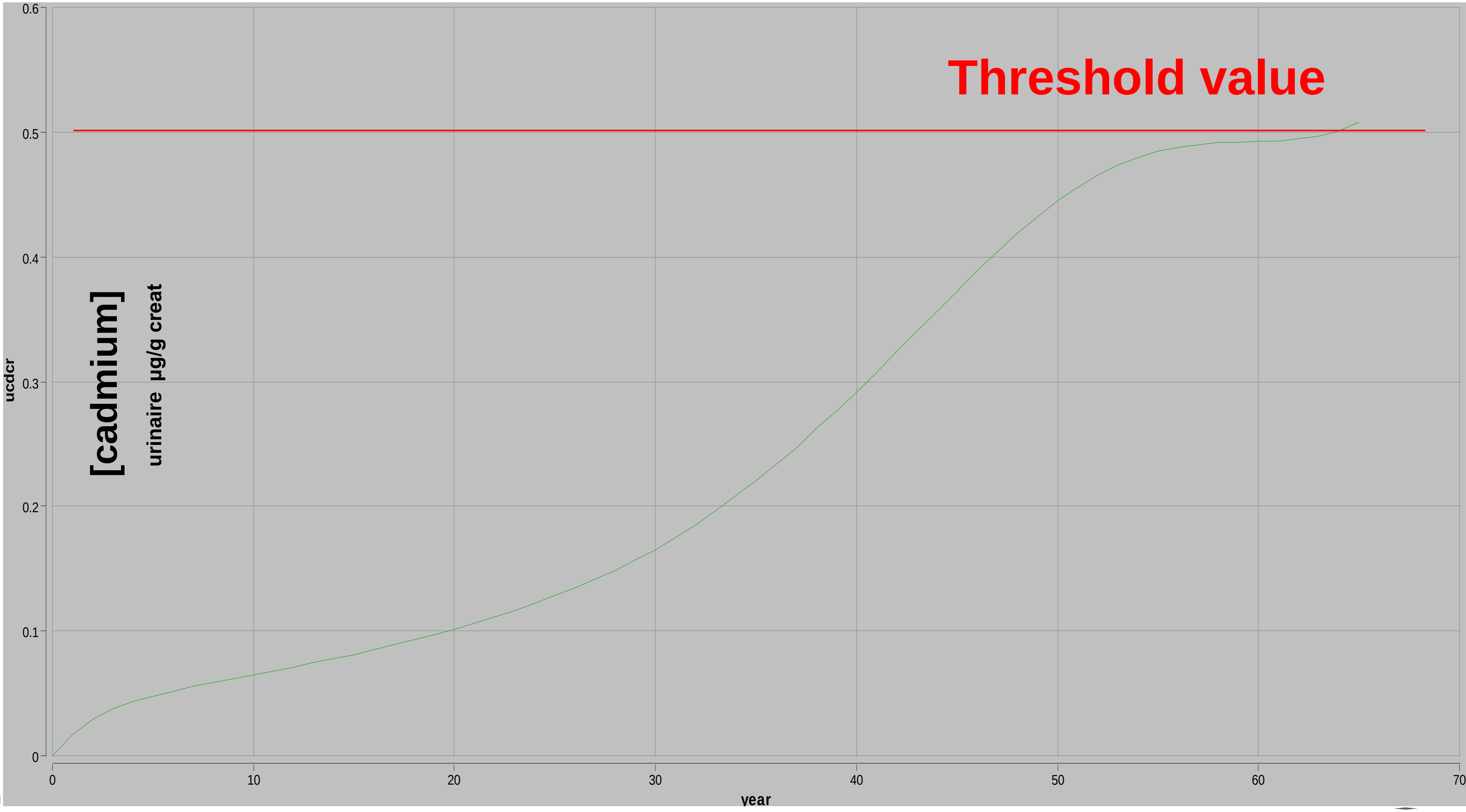


Urinary excretion of creatinine: depending on body weight and ages

age (year)	Urinary creatinine excretion in g per day				Body weight in Kg	
	estimated	measured	95 percentile	5 percentile	measured	estimated
3	0.17	0.23	0.32	0.16	15	16
4 to 5	0.27	0.32	0.45	0.22	19	22
6 to 8	0.49	0.49	0.64	0.38	25	31
9 to 13	0.86	0.75	1.02	0.41	37	42
14 to 18	1.28	1.46	2.14	0.85	65	54
		Based on Remer et al. 2002				

Usual Values		
Man	1.2-2	1.6
Woman	0.9-1.8	

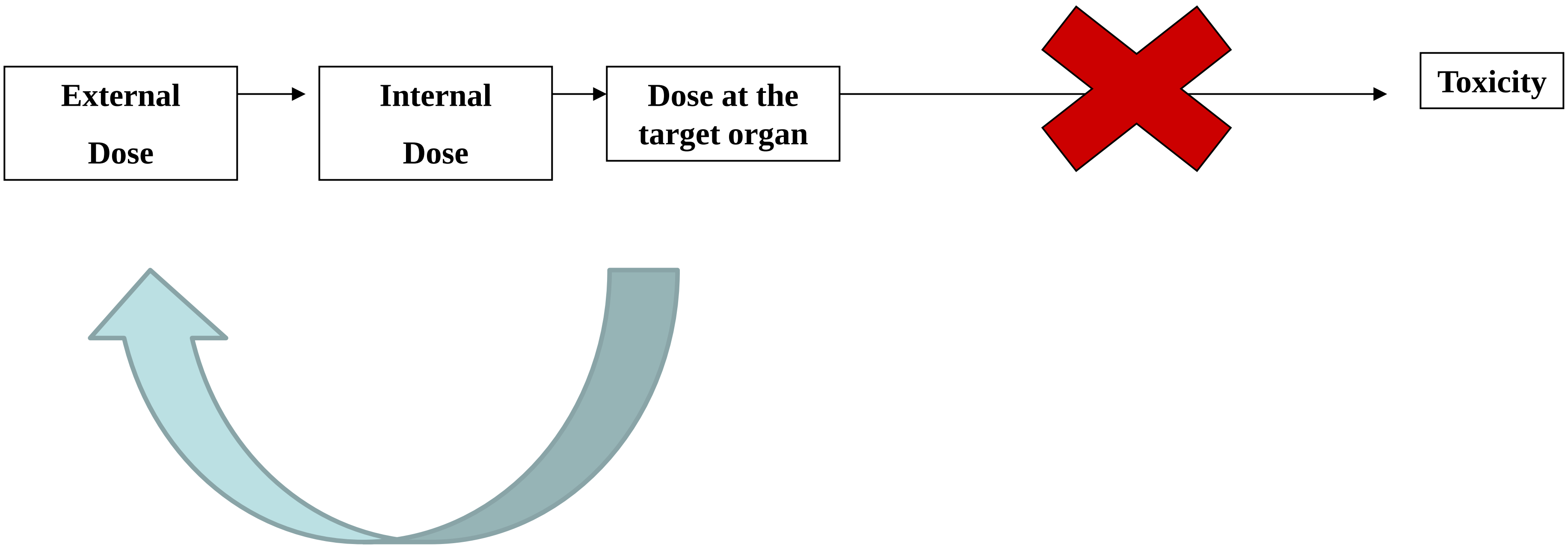
Urinary Cd evolution



Urinary Cd evolution

Age (years)	Urinary Cd in µg/g creatinine	Estimated body weight	Creatinine Excretion in 24 hours in g
1	0.02	8	0.06
3	0.04	16	0.17
4	0.04	20	0.23
…….	……	……	……
10	0.06	40	0.77
15	0.08	52	1.21
20	0.10	61	1.53
….	…..	….	….
30	0.16	71	1.68
40	0.29	73	1.38
50	0.44	71	1.10
65	0.51	69	1.07

Cadmium-reverse dosimetry

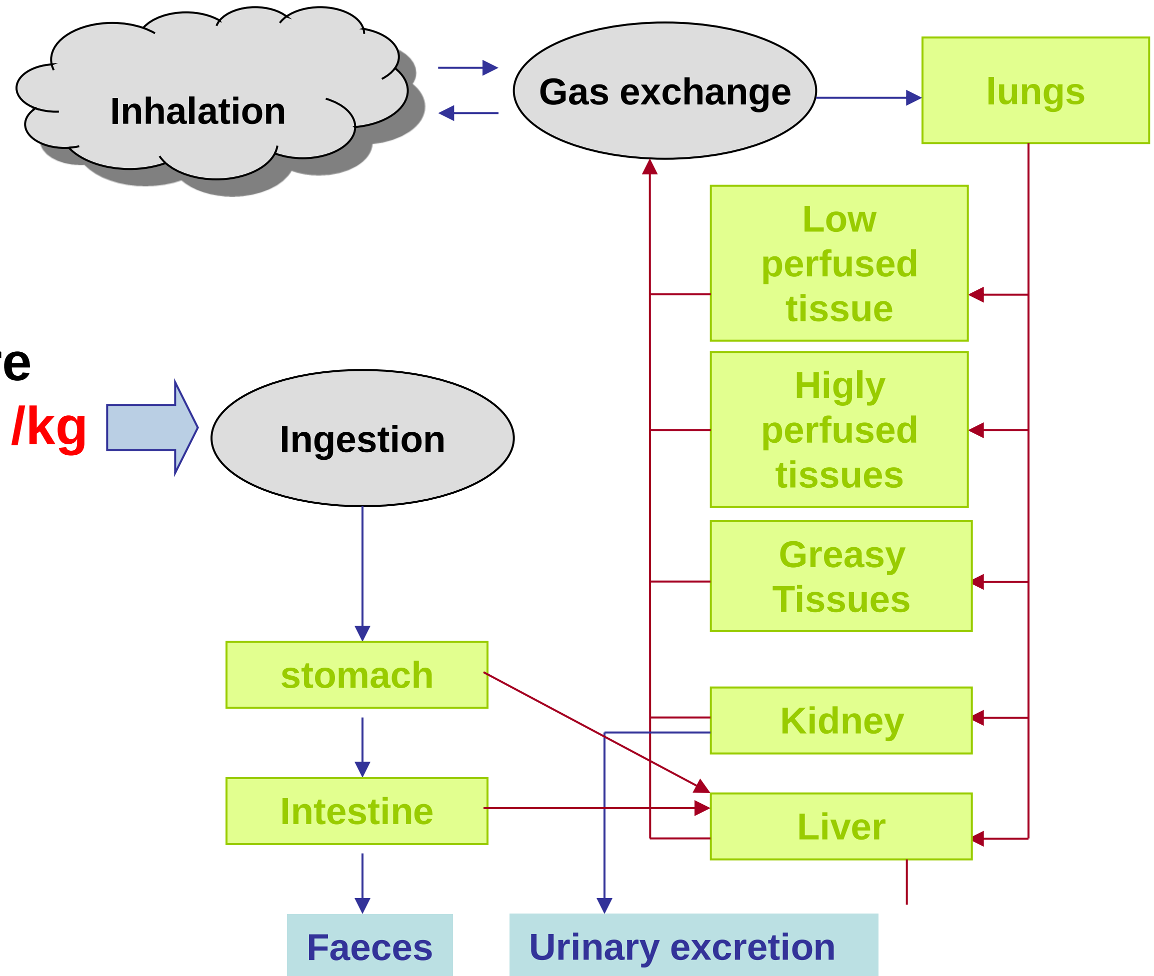


PB-PK modeling

PBPK Model

All life exposure

0.35 µg Cd /kg bw/day



not to be above 0.5 µg/g creat at 50 years old

Risk assessment and limits values in fertilizers

Conceptual Scheme

Modelisation

Cadmium inflow due to fertilizer materials

Various scenarios of soils fertilization

- fertilizer materials :

1) 100% mineral -> **Phosphate fertilizers** (major source)

2) Organic origin or combination of mineral and organic

- Cultures: selection of cultures that are representatives of the French exposure
- French situations -parameters influencing Cd transfer: Geochemical background, pH, organic material, clay, carbone
- Annual precipitations, yields

Determination of Cd contamination in agricultural soils

-> « Mass-Balance » approaches

[Cd]sol,i = [Cd]sol,i-1 + (Cd flux soil input– Cd flux soil output) / soil density

Determination of Cd contamination in cultures

-> Soil to Plant transfer Modelization

French specificities

updated ANSES model : Cd concentration variations in the wheat grain and potatoes

Determination of Cd leaching

-> Soil- leaching transfer Modelization

Conta : $\mu_{conta\ modèle}$ -x% → μ_{EAT2}-x%

Consumer exposure

$$E_i = \sum_{k=1}^{n} \frac{C_{i,k} \times L_k}{PC_i}$$

Risk Assessment

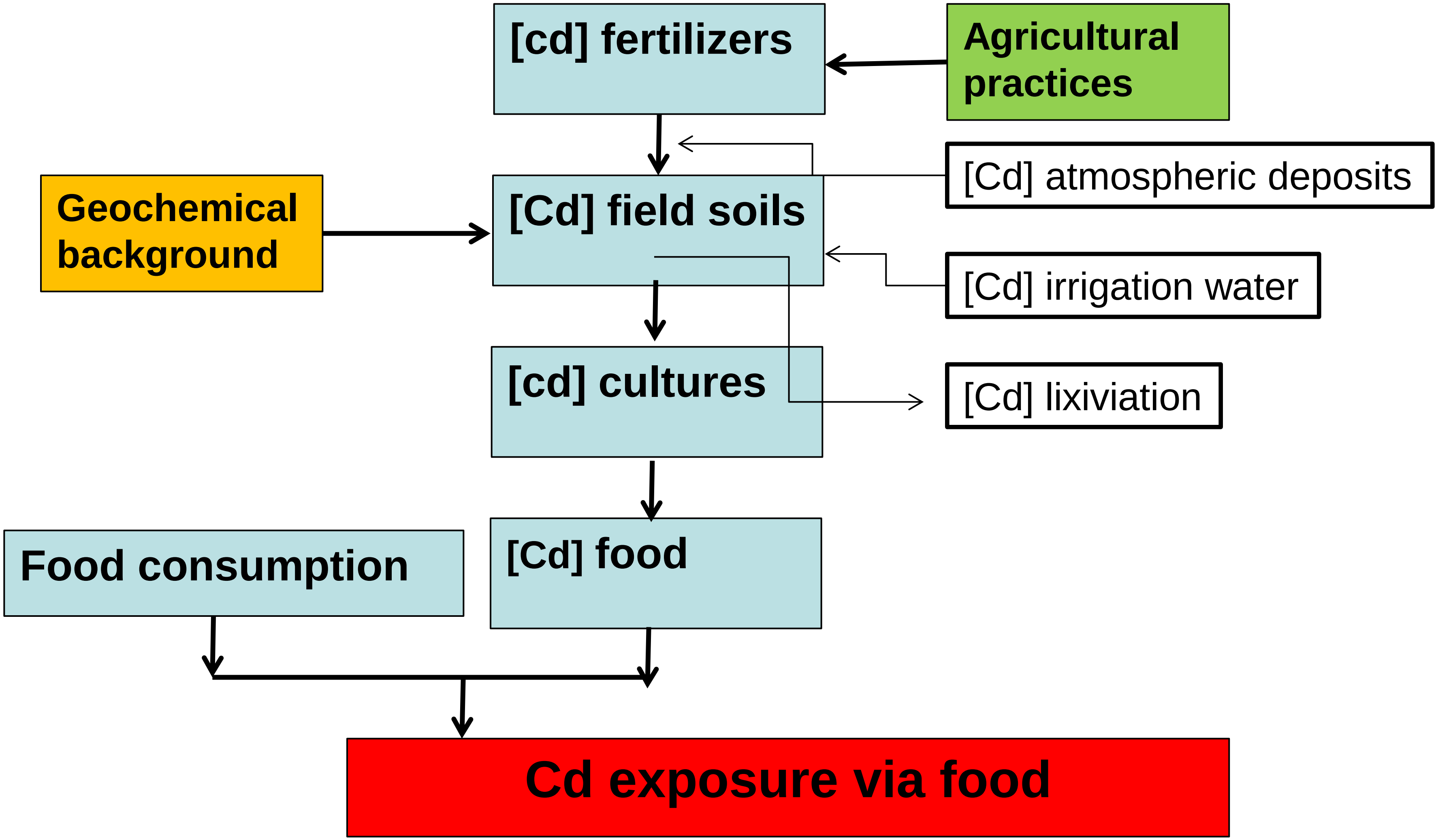
Toxicological Reference value

99 years projection time

Monte-Carlo Simulations (10 000 parcelles)

→ R-shiny

Conceptual Model



Selection of Cd inflow *via* fertilizing materials

Phosphate fertilizers

On-going discussions at EU level on the limits

Culture	annual Inflow (kg $P_2O_5.ha^{-1}$)	Inflow every 3 years (kg $P_2O_5.ha^{-1}$)
Wheat monoculture	80	100
Rotation potatoes/wheat/wheat	100	180

Based on recommendations concerning Phosphate inflow COMIFER

X

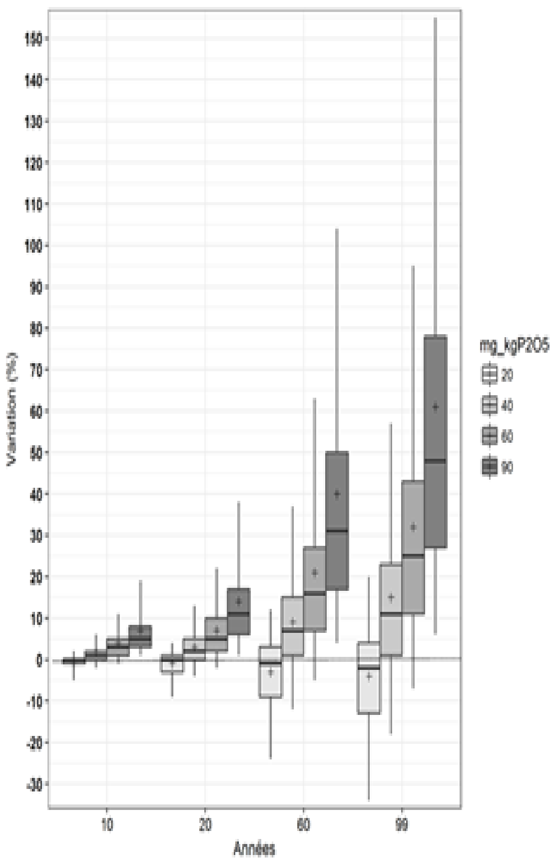
Concentration of Cd in phosphate fertilizers		99 years projection time			
	Limits (mg. kg $P_2O_5^{-1}$)	90	60	40	20
	Progressive reduction (mg. kg $P_2O_5^{-1}$)	years 1 to 3	years 4 to 15	years 16 to 99	
		60	40	20	

20 scenarios with or without culture rotation

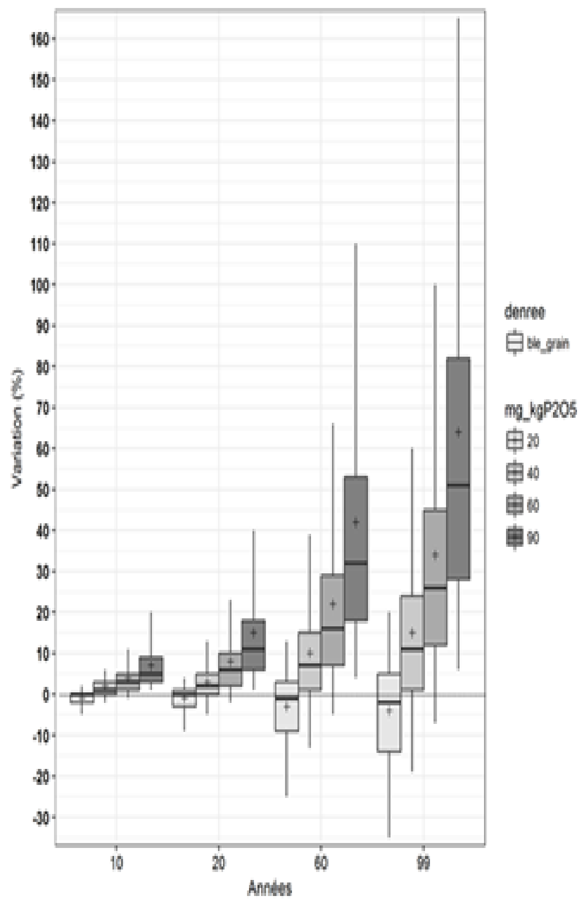
+

Inflow from organic fertilizers : **Livestock effluents, Sludge, Compost**

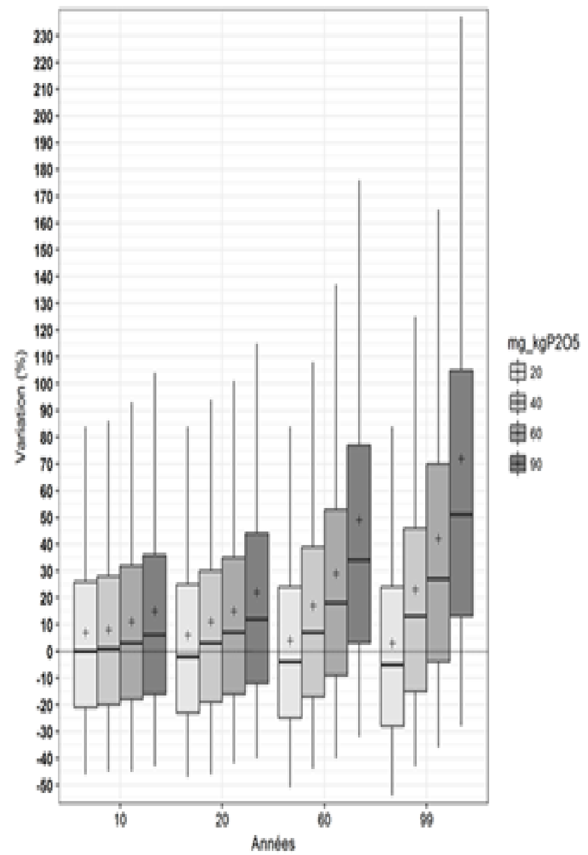
Tools output and hypothesis



Matrice sol



Matrice culture (grain de blé)



Matrice lixiviat

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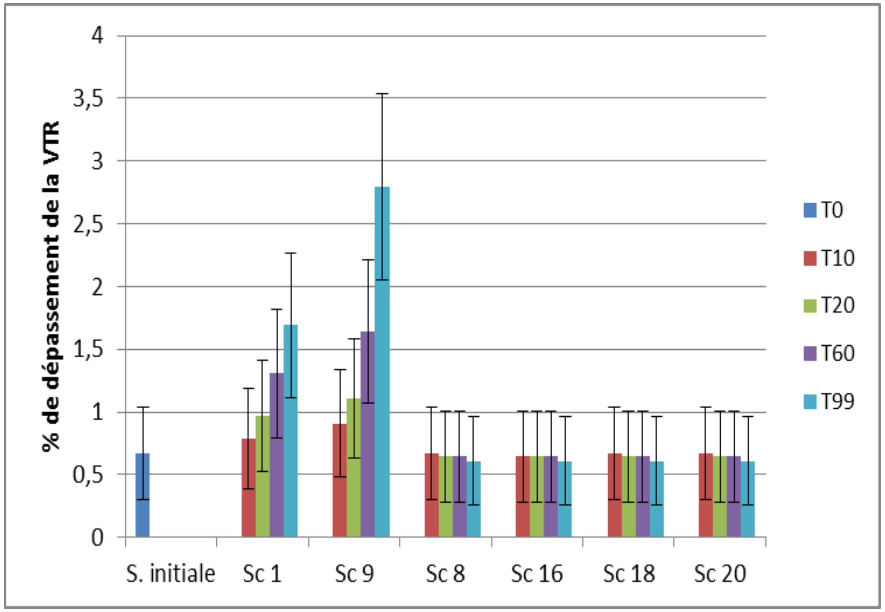
Tools output: some illustrations

Example: based on previous hyptohesis

Soil		Culture (wheat seed)	
Estimated (2018)	RMQS-GIS SOL	Estimated (2018)	PS/PC (2010-2015)
P50	P50	P50	P50
0.2 mg/kg	0.19 mg/kg	0.07 mg/kg	0.02 mg/kg

→ The output data of the model allow derivation of the adult and child consumer's average chronic exposure and 95th percentile, as a function of the projection time of the modelisation (10, 20, 60, 99 years), in correlation with the study of the evolution of the Cd contamination in crops (wheat grain and potato) linked to fertilization scenarios. These data have then to be compared with measured data to check if the model provides a predictive support to estimate Cd levels in the plants and in the final related food products

Preliminary Results



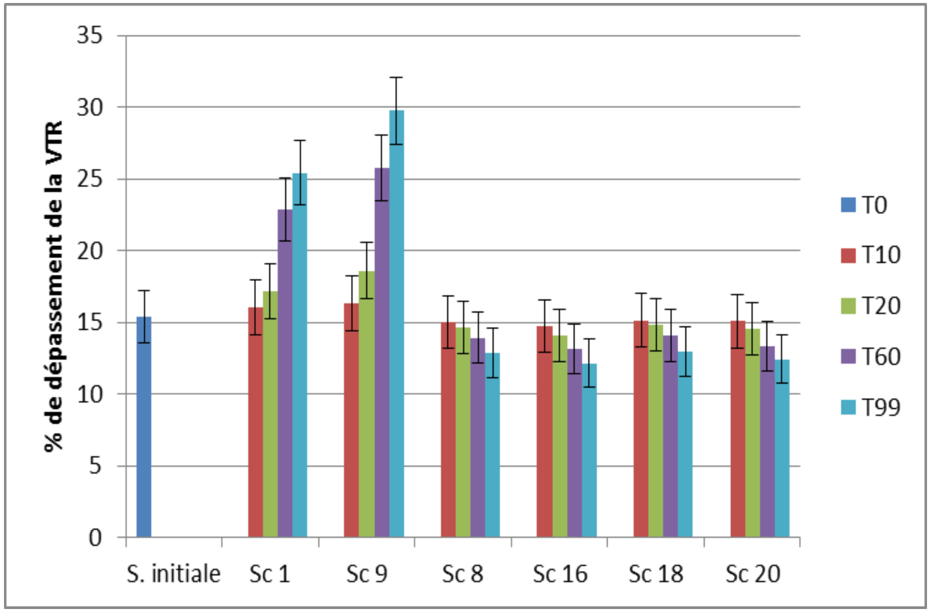
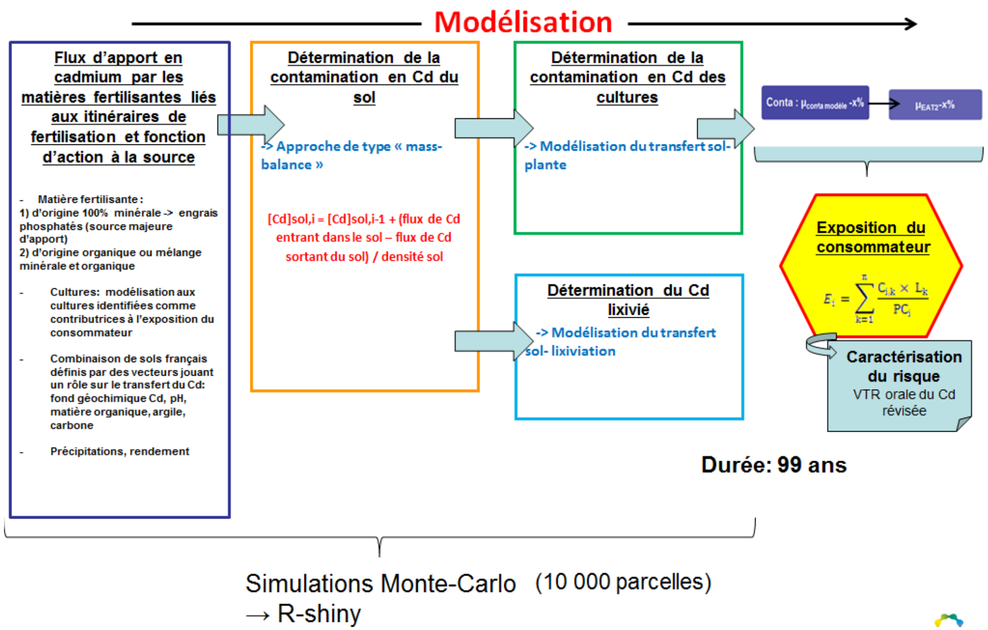


Figure 9. % of exceedance of the TRV of 0.35 µg Cd.kg b.w^{-1}.d^{-1} (IC$_{95\%}$) based on the various scenarios, in adults (on the left panel) and children (in the right panel), in LB.

S.initiale: initial situation : current exposure as the one published in EAT2 study (Anses, 2011a), with the TRV of 0.35 µg Cd.kg b.w^{-1}.d^{-1}

Sc1-Sc20: various scenarios

Conclusions & Perspectives



→ These mathematical models (from field to fork) are useful tools to support the risk assessment and decison making processes. Based on such simulations, acceptable levels of cadmium pollution in fertilizers, soils and at the end food items may be determined

→ These tools may also be used to identify data gaps and the more sensitive parameters which need to be better documented to have more robust estimations

Thank you for your attention !

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