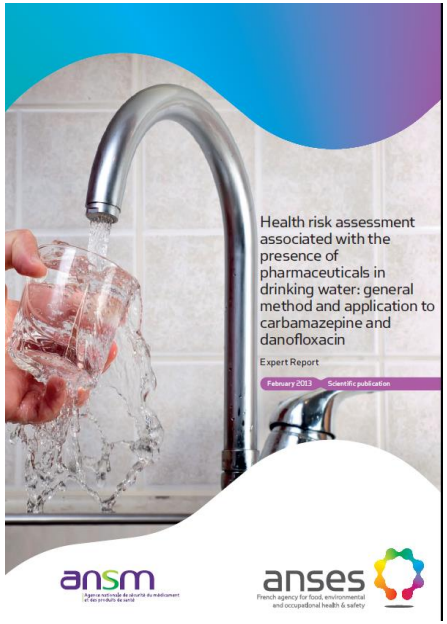
Health Risk Assessment of pharmaceuticals in drinking water in France



ICRAPHE

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Origin of works and Partners

Requests by the Ministry of Health (2006 - 2009)
Internal requests (2013 and 2016)

ANSES

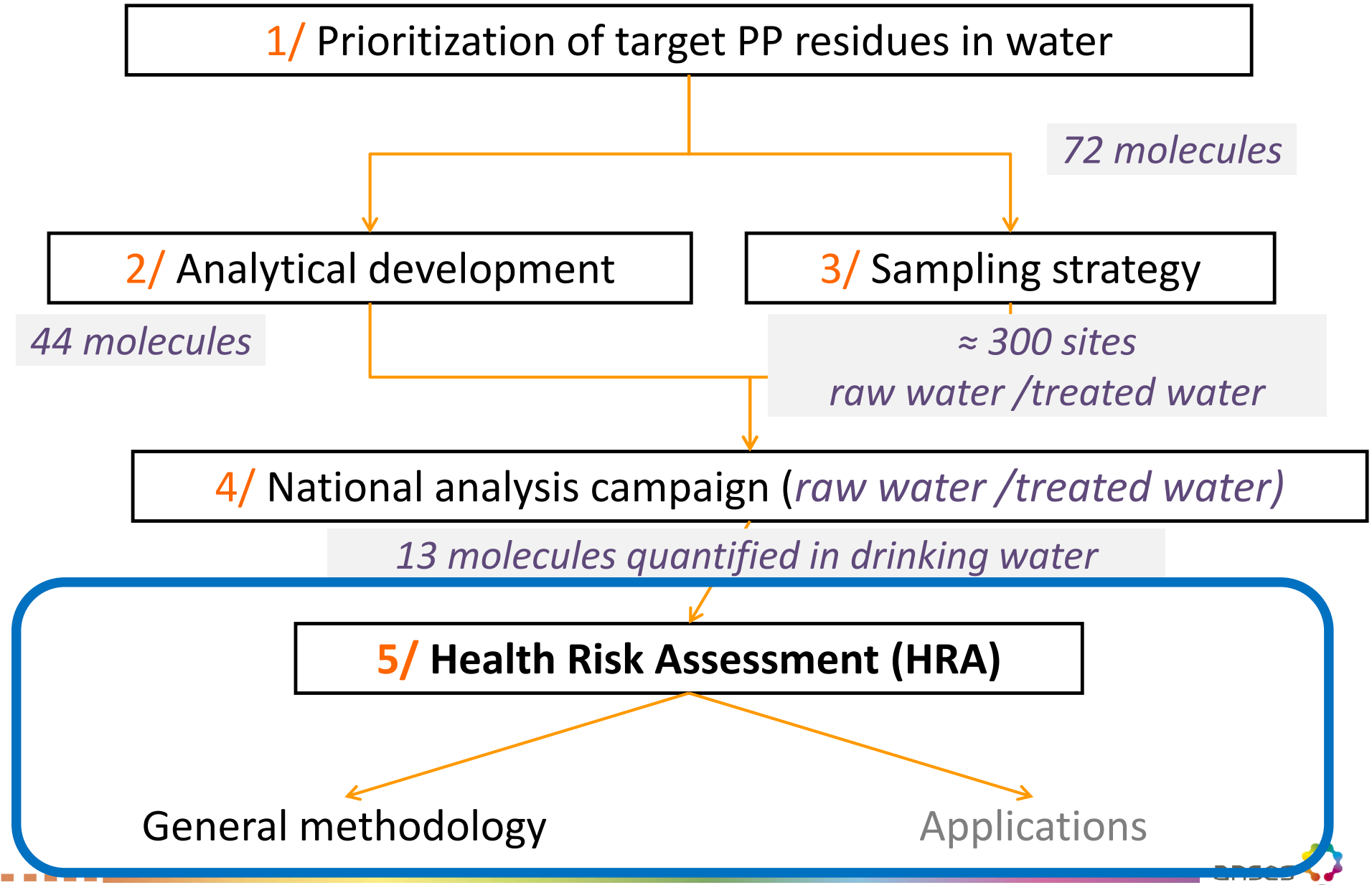
- Water risk assessment unit
- Hydrology laboratory (Nancy)
- Veterinary medicinal products laboratory (Fougères)
- French Agency for Veterinary Medicinal Products (ANMV)

ANSM

Contribution of the pharmaceutical industry

- **Leem** (Association of human PP manufacturers)
- **SIMV** (Association of veterinary PP manufacturers)

5 phases


1/ Prioritization of target PP residues in water
72 molecules
2/ Analytical development
44 molecules
3/ Sampling strategy
≈ 300 sites
raw water /treated water
4/ National analysis campaign (raw water /treated water)
13 molecules quantified in drinking water
5/ Health Risk Assessment (HRA)
General methodology
Applications

Collective expert appraisal

- Expert committee « Water »
- Specific working groups
- Others experts

Health Risk Assessment (HRA) Methodology

- Based on the usual HRA applied to contaminants in drinking water (WHO 2011; Afssa 2007)
- Taking into account characteristics of human and veterinary pharmaceuticals
- Method offering several alternatives depending on available data
- Intentionally very conservative
- Determination of guideline values (GV)

HRA Methodology

- **STEP 1** : Physical and chemical characterization
- **STEP 2** : Identification of relevant metabolites
- **STEP 3**: Identification of relevant transformation products
- **STEP 4** : Exposure assessment through drinking water
- **STEP 5** : Biological effects
- **STEP 6** : Selection of a human toxicity value
- **STEP7** : Determination of guideline value
- **STEP 8** : Health risk assessment

Determination of a GV in drinking water (1/4)

Step 6.1 – Existing toxicity reference value (s) * (TRV) ?

* ADI (Acceptable daily intake)- TDI (Tolerable daily intake)

Yes

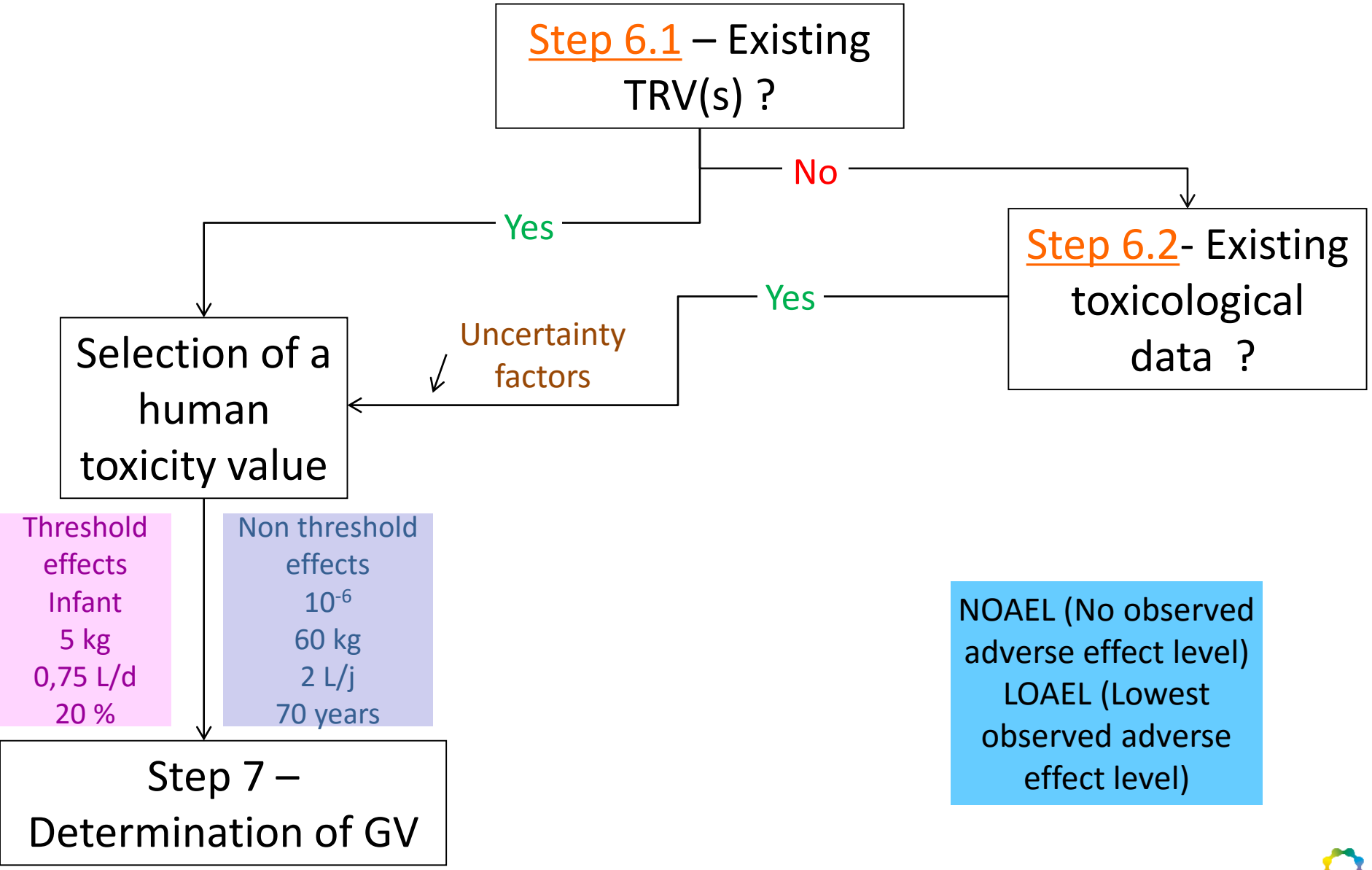
Selection of a human toxicity value

Threshold effects
Infant
5 kg
0,75 L/d
20 %

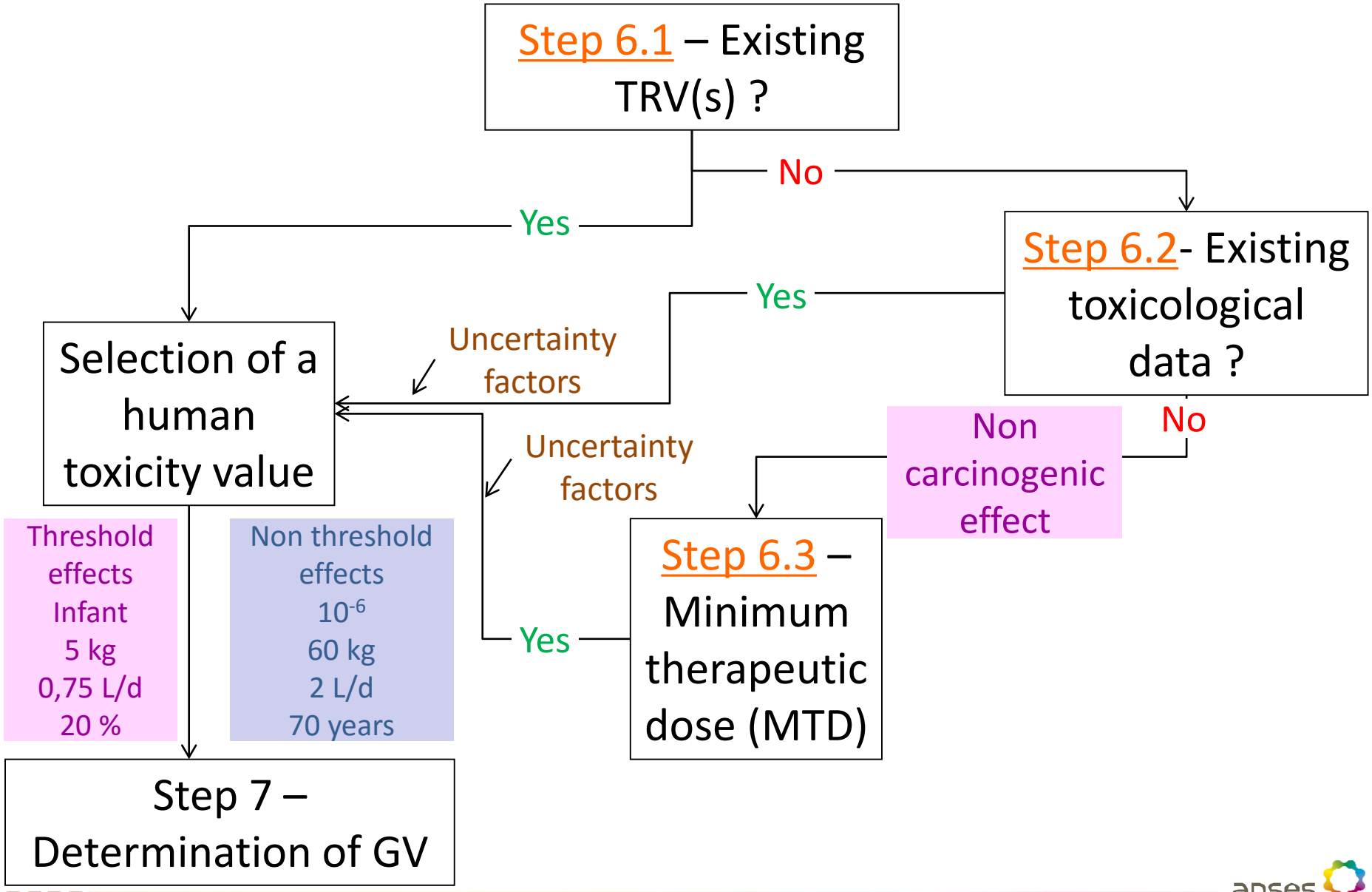
Non threshold effects
10^{-6}
60 kg
2 L/d
70 years

Step 7 – Determination of GV

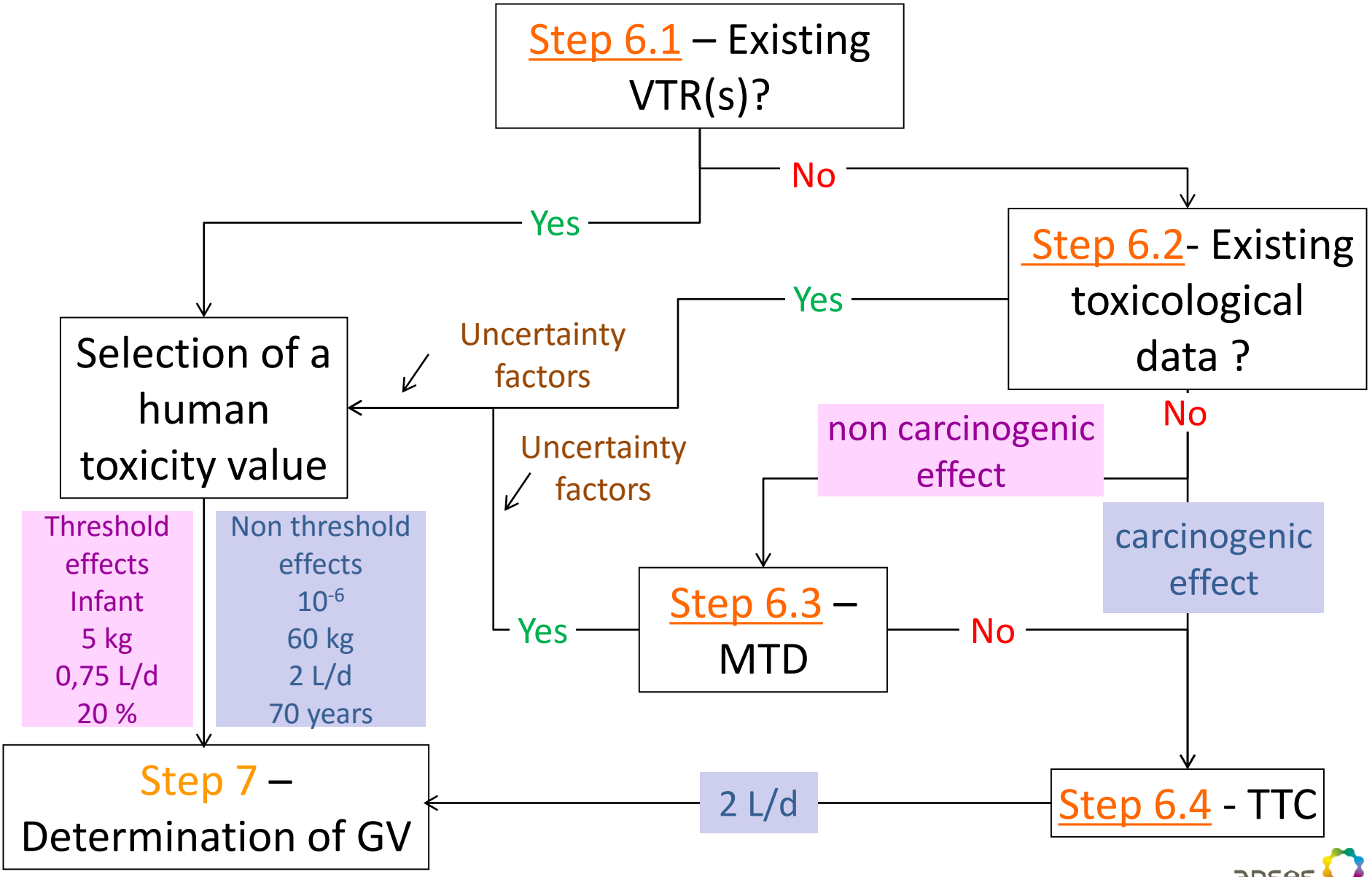
Determination of a GV in drinking water (2/4)



Determination of a GV in drinking water (3/4)



Determination of a GV in drinking water (4/4)



HRA methodology

- **STEP 1** : Physical and chemical characterization
- **STEP 2** : Identification of relevant metabolites
- **STEP 3**: Identification of relevant transformation products
- **STEP 4** : Exposure assessment through drinking wat
- **STE**
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- **STE**

Safety Margin (SM)

$SM = GV/C_{DW}$

If MS > 1, the risk is regarded as negligible

- **STEP 8** : Health risk assessment

Guideline values and HRA

Carbamazepin + 10,11 epoxycarbamazepin

TRV selection Method	Population	TRV	Body weight (kg)	Water consumption per day (L)	Share of TRV attributed to DW intake	GV (µg/L)
Toxicological studies	Adult	TRV_{tox} = 25 µg/kg	60	2	20 %	GV_{tox} = 150
	Child		10	1		GV_{tox} = 50
	Infant		5	0.75		**GV_{tox} = 33**

$$SM = \frac{GV}{C._{max}} = \frac{33}{0.04} = 825$$

SM > 1 : risk is considered to be negligible

6 pharmaceuticals

Molecules	Percentage of detection (% > LoD)	Maximum concentration (ng/L)		GV (ng/L)	SM	
10,11-epoxycarbamazepin	14.8	6	40	33 000	**825**	**Tox. data**
Carbamazepin	9	33				
2 hydroxyibuprofen	5.8	85		-		
Carboxyibuprofen	-	-		-		
Ibuprofen	1.4	traces		33 000	**3300**	**Tox. data**
Ketoprofen	0.4	36		2700	**75**	**Tox. data**
Vet **Danofloxacin**	3.5	57		32 000	**561**	**VTR**
Demethyldanofloxacin	-	-		3 000	-	**VTR**
Vet **Tylosin**	2.2	20		667 000	**33 350**	**VTR**
Vet **Florfenicol**	0.4	traces		1 300	**26**	**VTR**

Experience feedback– Points in common

Advantages

- Molecules well characterized
  - Physico-chimical properties
  - ADME including identification of main metabolites
- Known effects on humans

Limitations

- Metabolites
  - Toxicity
- Transformation products
  - Identification
  - Toxicity
- Use of TTC

Experience feedback

Veterinary pharmaceuticals

Advantages

- Known effects on humans for the production animals
  - Public abstract
  - Detail of NOAELs
  - Existence of TRV

Limitations

- Impossible to use the MTD
- Access to details of MRL dossiers

Human pharmaceuticals

Advantages

- Known effects on humans at therapeutic doses
  - ADME
  - Therapeutic effects
  - Undesirable effects
  - Existence of a MTD

Limitations

- Access to data
  - Toxicological studies
- Determination of TRV
  - Details of toxicity studies
  - Use of MTD

Conclusions

- Negligible health risk associated with the ingestion of evaluated molecules *via* drinking water, considering the available analytical and toxicological data
- Availability of data is a very limiting factor for HRA
- Need for **chronic** toxicity studies on pharmaceuticals, their metabolites and transformation products
- The pharmaceuticals are assessed individually, what about mixtures?
- The issue of health effects of low doses
- Further works on Diclofenac and others pharmacological groups : oxazepam et paracetamol

Reports available on: www.anses.fr

- *Hiérarchisation des résidus de médicaments d'intérêt pour l'analyse des ressources et des eaux traitées* [Prioritisation of target pharmaceutical product residues to be detected in source and treated water] *(**november 2008**)*

- *Campagne nationale d'occurrence des résidus de médicaments dans les eaux destinées à la consommation humaine* [National sampling survey related to the pharmaceuticals in drinking water] *(**march 2011**)*

- *Health risk assessment associated with the presence of pharmaceuticals in drinking water: general method and application to carbamazepine and danofloxacin (**february 2013**)*

- *Evaluation des risques sanitaires liés à la présence de tylosine ou florfénicol dans les eaux destinées à la consommation humaine* [[Health risk assessment associated with the presence of tylosin or florfenicol in drinking water] *(**february 2014**)*

- *Evaluation des risques sanitaires liés à la présence de Kétoprofène ou d'ibuprofène dans les eaux destinées à la consommation humaine* [[Health risk assessment associated with the presence of ketoprofen or ibuprofen in drinking water] *(**march 2015**)*

THANKS FOR YOUR ATTENTION