Regulatory Toxicology and Pharmacology 62 (2012) 41–48

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Assessment of the health risks related to the presence of drug residues in water for human consumption: Application to carbamazepine

Paul Houeto [a,*], Aude Carton [a], Michel Guerbet [b], Anne-Cécile Mauclaire [a], Chantal Gatignol [c], Philippe Lechat [a], Dominique Masset [a]

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CONTEXT AND OBJECTIVE OF THE STUDY?

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OBJECTIVE:

Taking into account that the occurrence of **pharmaceutical residues in water intended for human consumption (WIHC)** is a common concern in the served populations, **we aimed to develop a general strategy in order to determine more precisely their safety concern through** three possible ways to approach this question, for individual chemicals.

We propose the following algorithm: **(1)** when there is human or animal toxicity data, a toxicity reference value (TRV) can be calculated; **(2)** when this is not applicable, an attempt should be made to derive the TRV using known information about the minimum therapeutic dose (MTD); and **(3)** when no applicable data is available, at all, a threshold of toxicological concern (TTC) should be estimated.

In order to apply and compare the different approaches and in addition whether there is a safety concern, we will use two compounds, carbamazepine and its major metabolite 10,11-epoxycarbamazepine resulting in a list of chemicals from a national sampling survey to model such an approach.

NATIONAL SAMPLING SURVEY?

1-Seletion criteria of molecules?

2-Number of molecules analysed?

3-Selection criterion of sites?

4-Focus on which drugs?

NATIONAL SAMPLING SURVEY

List of 76 priority molecules
according criteria (tonnage, solubility, activity)

45 molecules
from different chemical families and therapeutic classes

238 sites
representative of ≈ 24 %
of population served

19 molecules
detected at least one

Choices of exposure concentrations ?

Table 1
Frequency of detection and quantification of different molecules in water intended for human consumption (Anses, 2011).

Molecules (n = 280 samples)	Frequency of quantifiable results (>LQ)	Minimum and Maximum content (ng/L)
Carbamazepine	**4.0 %**	5–33
Epoxycarbamazepine	7.6%	1–6

LQ, limit of quantification (1–50 ng/L); n, number of samples.

NATIONAL SAMPLING SURVEY

List of 76 priority molecules
according criteria (tonnage, solubility, activity)

45 molecules
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Choices of
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The highest !

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Carbamazepine	**4.0 %**	5–33
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LQ, limit of quantification (1–50 ng/L); n, number of samples.

RISK ASSESSMENT PROCEDURE

(1) TRV_{Tox}

The Toxicity Reference Value (TRV) approach?

Calculated value?

Data used?

Limits?

(2) TRV_{MTD}

The Minimum Therapeutic Dose (MTD) approach?

Calculated value?

Data used?

Limits?

(3) TTC

The Threshold of Toxicological Concern (TTC) approach?

Calculated value?

Data used?

Limits?

RISK ASSESSMENT PROCEDURE

(1) TRV_{Tox}

The Toxicity Reference Value (TRV) approach?

Calculated value?

Toxicological approach based on NOAEL/LOAEL/BMDL

Data used?

Pharmaco-toxicological studies from the marketing authorization dossier or literature data

Limits?

lack of data, especially in the case of metabolites and old molecules

(2) TRV_{MTD}

The Minimum Therapeutic Dose (MTD) approach?

Calculated value?

Data used?

Limits?

(3) TTC

The Threshold of Toxicological Concern (TTC) approach?

Calculated value?

Data used?

Limits?

RISK ASSESSMENT PROCEDURE

(1) TRV_{Tox}

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Data used?

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Limits?

lack of data, especially in the case of metabolites and old molecules

(2) TRV_{MTD}

The Minimum Therapeutic Dose (MTD) approach?

Calculated value?

MTD used as the point of departure in assessing potential health hazards from pharmaceutical drug residues in drinking water

Data used?

From the marketing authorization dossier

Limits?

Cannot be generalised, especially to certain families of molecules (cytotoxic agents, hormones, allergens, antibiotics, metabolites)

(3) TTC

The Threshold of Toxicological Concern (TTC) approach?

Calculated value?

Data used?

Limits?

RISK ASSESSMENT PROCEDURE

(1) TRV_{Tox}

The Toxicity Reference Value (TRV) approach?

Calculated value?

Toxicological approach based on NOAEL/LOAEL/BMDL

Data used?

Pharmaco-toxicological studies from the marketing authorization dossier or literature data

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(2) TRV_{MTD}

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Data used?

From the marketing authorization dossier

Limits?

Cannot be generalised, especially to certain families of molecules (cytotoxic agents, hormones, allergens, antibiotics, metabolites)

(3) TTC

The Threshold of Toxicological Concern (TTC) approach?

Calculated value?

0.15 µg/person/day (excess risk of 10^{-6})

human exposure dose below which the risk is believed to be sufficiently low to exempt a substance from toxicological investigations

Probabilistic approach based on the concept of structural similarity

Data used?

built from a database of known carcinogenic substances

Limits?

Only dedicated to substances for which there is no available data, but allows to be freed from the marketing authorization dossier and cover the uncertainties related to the carcinogenic properties

RISK ASSESSMENT PROCEDURE

(1) TRV_{Tox}

The Toxicity Reference Value (TRV) approach?

Calculated value?

Toxicological approach based on NOAEL/LOAEL/BMDL

Data used?

Pharmaco-toxicological studies from the marketing authorization dossier or literature data

Limits?

lack of data, especially in the case of metabolites and old molecules

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The Minimum Therapeutic Dose (MTD) approach?

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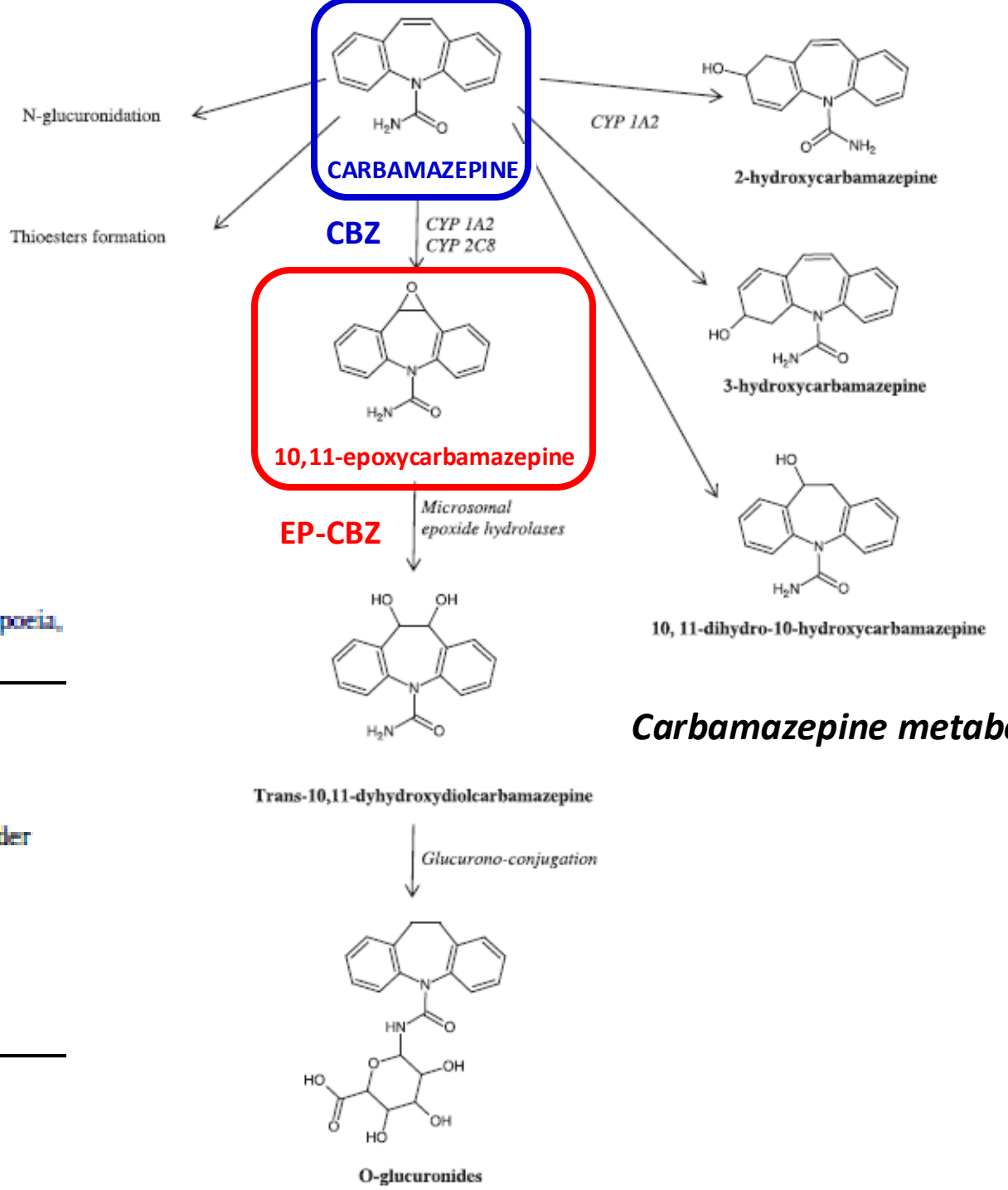
PHARMACOLOGY - PHARMACOKINETICS

Table 2
Physico-chemical parameters of carbamazepine (Inchem 1999; US Pharmacopoeia, 2008).

CAS No.	298-46-4
ATC No.	N03AF01
Chemical formula	$C_{15}H_{12}N_2O$
Molecular weight	236.27 g mol^{-1}
Presentation	White to yellowish-white crystalline powder
Solubility in water	112.1 mg/L
Vapour pressure	1.84×10^{-7} mm Hg (25 °C)
Melting point	190 to 193 °C
Henry's law constant	1.08×10^{-10} atm m^3 mol^{-1} (25 °C)
pKa	13.9
Log K_{ow}	2.45



Carbamazepine metabolism

TOXICOLOGY DATA

- **Toxicity?**
  - **Rats:** LOAEL from 50 to 200 mg/kg/day
  - **Dogs:** NOAEL from 50 to 100 mg/kg/day and LOAEL from 100 to 300 mg/kg/day
  - **Humans:** LOAEL = 10 mg/kg/day
- **Mutagenicity?**
  - ***In vitro* and *in vitro* studies:** non-mutagenic
- **Carcinogenicity?**
  - **Rats:** a 2 years study in Sprague–Dawley rats at doses of 25, 75 and 250 mg/kg/day
    - increase in the incidence of hepatocellular tumours in females
    - benign testicular interstitial cell adenomas in males

    } starting at doses of 25 mg/kg/day
  - **NTP, IARC, FDA:** not classified as carcinogenic
- **Effects on reproduction function?**
  - **Rats:** LOAEL from 192 to 250 mg/kg/day
  - **Mice:** NOAEL = 192 mg/kg/day
  - **Rabbits:** LOAEL = 250 mg/kg/day
  - **Humans:** LOAEL from 3 to 11 mg/kg/day

HEALTH RISK ASSESSMENT

Drinking Water Equivalent Level:

$$DWEL = \frac{TRV \times Body\ Weight\ (BW)}{water\ Ingestion\ Rate\ (IR)}$$

DWEL: concentration of a pharmaceutical / L of water that does not result in significant risk to the health of consumers over a lifetime of 70 years

Adult IR = 2 L/day (BW=60 kg)

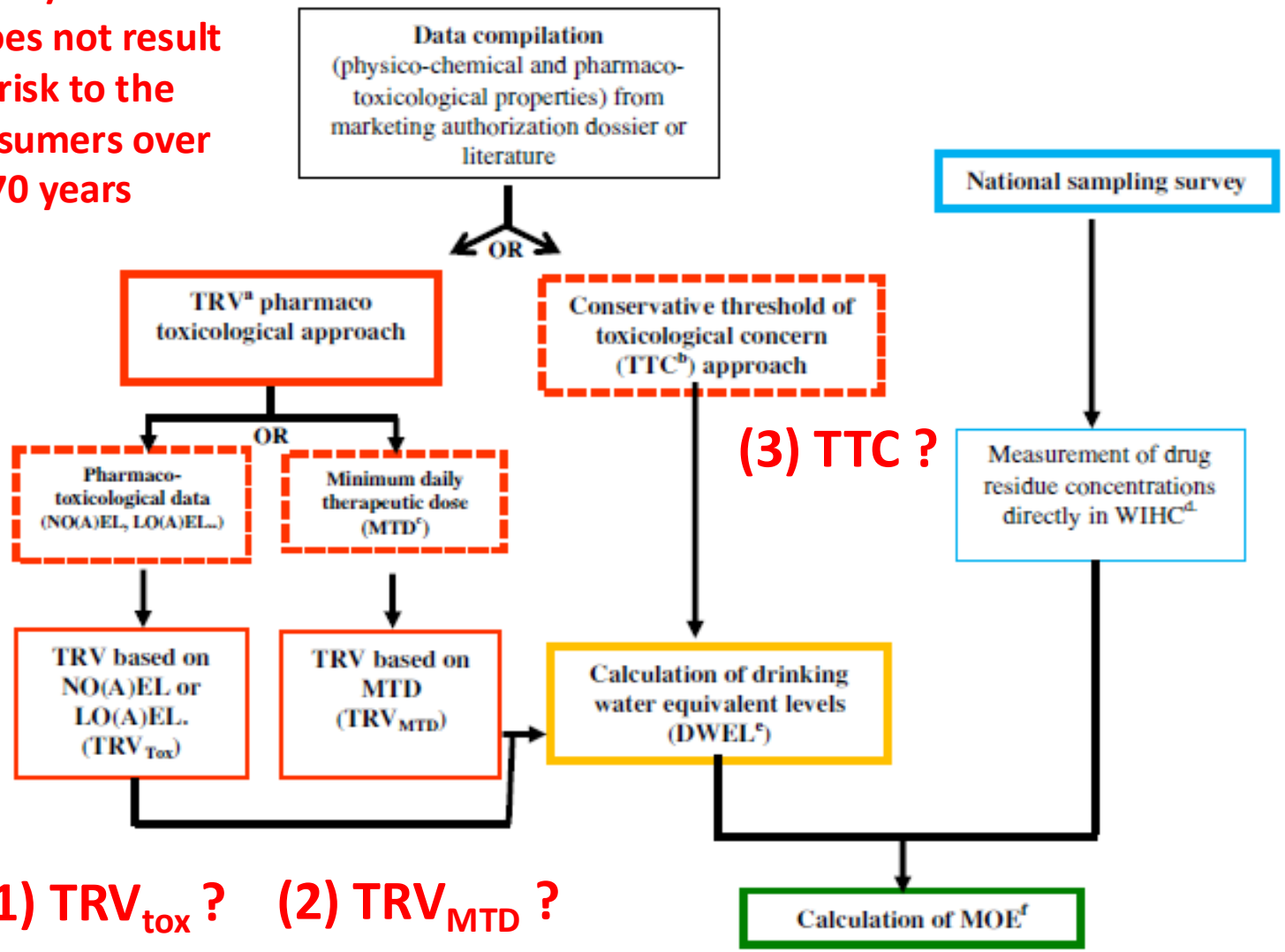
Children IR = 1 L/day (BW=16,7 kg)

Lifelong consumption = 70 years

Margin Of Exposure:

$$MOE = \frac{DWEL}{Concentration\ (C_{CBZ}\ or\ C_{EP\text{-}CBZ})}$$

Different methodological approaches for health risk assessment of drug residues in water intended for human consumption



HEALTH RISK ASSESSMENT BY TRV TOXICOLOGICAL APPROACH

- **Reports from toxicity studies?**
  - **Rats:** LOAEL from 50 to 200 mg/kg/day
  - **Dogs:** NOAEL from 50 to 100 mg/kg/day and LOAEL from 100 to 300 mg/kg/day
  - **Humans:** LOAEL = 10 mg/kg/day
- **Mutagenicity?**
  - ***In vitro* and *in vitro* studies:** non-mutagenic
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  - **Rabbits:** LOAEL = 250 mg/kg/day
  - **Humans:** LOAEL from 3 to 11 mg/kg/day

(1) Choices for TRV_{tox} calculation:

Critical effect?

Critical dose?

HEALTH RISK ASSESSMENT BY TRV TOXICOLOGICAL APPROACH

- **Toxicity?**
  - **Rats:** LOAEL from 50 to 200 mg/kg/day
  - **Dogs:** NOAEL from 50 to 100 mg/kg/day and LOAEL from 100 to 300 mg/kg/day
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  - **Rabbits:** LOAEL = 250 mg/kg/day
  - **Humans: LOAEL from 3 to 11 mg/kg/day**

(1) Choices for TRV_{tox} calculation:

Critical effect: on reproduction function

Critical dose: 3 mg/kg/day (200 mg/day)

HEALTH RISK ASSESSMENT BY TRV TOXICOLOGICAL APPROACH

(1) Choices for TRV_{tox} calculation:

Critical effect: on reproduction function

Critical dose:

LOAEL = 3 mg/kg/day (200 mg/day)

Uncertainty Factors?

UF_L ?
LOAEL-to-NOAEL

UF_S ?
Short-term to long-term exposure

UF_A ?
Animal to Human

UF_H ?
Average Human to Sensitive Human

UF_D ?
Database Insufficiency

MF ?
Modifying Factor

HEALTH RISK ASSESSMENT BY TRV TOXICOLOGICAL APPROACH

(1) Choices for TRV_{tox} calculation:

Critical effect: on reproduction function

Critical dose:

LOAEL = 3 mg/kg/day (200 mg/day)

Uncertainty Factors:

Global **UF =** 3x1x1x3x10x10 = **900**

UF_L = 3
LOAEL-to-NOAEL

UF_S = 1
Short-term to long-term exposure

UF_A = 1
Animal to Human

UF_H = 3
Average Human to Sensitive Human

UF_D = 10
Database Insufficiency

MF = 10
Modifying Factor

HEALTH RISK ASSESSMENT BY TRV TOXICOLOGICAL APPROACH

(1) Choices for TRV_{tox} calculation:

Critical effect: on reproduction function

Critical dose:

LOAEL = 3 mg/kg/day (200 mg/day)

Uncertainty Factors:

Global **UF = 900**

TRV_{Tox}?

UF_L = 3
LOAEL-to-NOAEL

UF_S = 1
Short-term to long-term exposure

UF_A = 1
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Average Human to Sensitive Human

UF_D = 10
Database Insufficiency

MF = 10
Modifying Factor

HEALTH RISK ASSESSMENT BY TRV TOXICOLOGICAL APPROACH

(1) Choices for TRV_{tox} calculation:

Critical effect: on reproduction function

Critical dose:

LOAEL = 3 mg/kg/day (200 mg/day)

Uncertainty Factors:

Global **UF = 900**

$$TRV_{Tox} = \frac{3}{900}$$

$$= 3.3 \times 10^{-3} \text{ mg/kg/day}$$

$TRV_{Tox} = 3.3 \times 10^{3}$ ng/kg/day

$UF_L = 3$
LOAEL-to-NOAEL

$UF_S = 1$
Short-term to long-term exposure

$UF_A = 1$
Animal to Human

$UF_H = 3$
Average Human to Sensitive Human

$UF_D = 10$
Database Insufficiency

$MF = 10$
Modifying Factor

HEALTH RISK ASSESSMENT BY TRV TOXICOLOGICAL APPROACH

DWEL ?
adults

DWEL ?
children

MOE ?
adults

MOE ?
children

HEALTH RISK ASSESSMENT BY TRV TOXICOLOGICAL APPROACH

$$\text{DWEL}_{\text{adults}} = \frac{TRV_{Tox} \times BW}{IR} = \frac{3.3 \times 10^3 \times 60}{2} = \frac{(ng/kg/day) \times kg}{L/day} = 99 \times 10^3 \text{ ng / L}$$

$$\text{DWEL}_{\text{children}} = \frac{TRV_{Tox} \times BW}{IR} = \frac{3.3 \times 10^3 \times 16{,}7}{1} = \frac{(ng/kg/day) \times kg}{L/day} = 55 \times 10^3 \text{ ng / L}$$

MOE ?
adults

MOE ?
children

HEALTH RISK ASSESSMENT BY TRV TOXICOLOGICAL APPROACH

$$\text{DWEL}_{\text{adults}} = \frac{TRV_{Tox} \times BW}{IR} = \frac{3.3 \times 10^3 \times 60}{2} = \frac{(ng/kg/day) \times kg}{L/day} = 99 \times 10^3 \text{ ng / L}$$

$$\text{DWEL}_{\text{children}} = \frac{TRV_{Tox} \times BW}{IR} = \frac{3.3 \times 10^3 \times 16{,}7}{1} = \frac{(ng/kg/day) \times kg}{L/day} = 55 \times 10^3 \text{ ng / L}$$

$$\text{MOE}_{\text{adults}} = \frac{\text{DWEL adult}}{C_{CBZ}} = \frac{99{,}000}{33} = \frac{ng/L}{ng/L} = 3000$$

$$\text{MOE}_{\text{children}} = \frac{\text{DWEL children}}{C_{CBZ}} = \frac{55{,}000}{33} = \frac{(ng/kg/day) \times kg}{L/day} = 1667$$

MOE calculated from DWEL and carbamazepine (CBZ) concentration found in WICH following the TRV toxicological approach

	Methods	DWEL (ng/L)		Margins of exposure (MOE)	
		Adults	Children	Adults	Children
Measured concentration of carbamazepine in WIHC = 33 ng/L	Toxicity reference value based on toxicological data (TRV_{Tox})	99,000	55,000	3000	1667

HEALTH RISK ASSESSMENT BY TOXICOLOGICAL APPROACH BASED ON MTD

(2) Choices for TRV_{MTD} calculation:

Critical dose? **MTD: 10 mg/kg/day**

For both adults and children

(French Health Products Safety Agency, 2011)

Uncertainty Factors?

UF_L ?

LOAEL-to-NOAEL

UF_S ?

Short-term to long-term exposure

UF_A ?

Animal to Human

UF_H ?

Average Human to Sensitive Human

UF_D ?

Database Insufficiency

MF ?

Modifying Factor

HEALTH RISK ASSESSMENT BY TOXICOLOGICAL APPROACH BASED ON MTD

(2) Choices for TRV_{MTD} calculation:

Critical dose? **MTD: 10 mg/kg/day**

For both adults and children

(French Health Products Safety Agency, 2011)

Uncertainty Factors?

Global UF = 3x3x1x3x3x10 **= 810**

UF_L = 3
LOAEL-to-NOAEL

UF_S = 3
Short-term to long-term exposure

UF_A = 1
Animal to Human

UF_H = 3
Average Human to Sensitive Human

UF_D = 3
Database Insufficiency

MF = 10
Modifying Factor

HEALTH RISK ASSESSMENT BY TOXICOLOGICAL APPROACH BASED ON MTD

(2) Choices for TRV_{MTD} calculation:

Critical dose? **MTD: 10 mg/kg/day**

For both adults and children

(French Health Products Safety Agency, 2011)

Uncertainty Factors?

Global UF = 810

TRV_{MTD}?

UF_L = 3
LOAEL-to-NOAEL

UF_S = 3
Short-term to long-term exposure

UF_A = 1
Animal to Human

UF_H = 3
Average Human to Sensitive Human

UF_D = 3
Database Insufficiency

MF = 10
Modifying Factor

HEALTH RISK ASSESSMENT BY TOXICOLOGICAL APPROACH BASED ON MTD

(2) Choices for TRV_{MTD} calculation:

Critical dose? **MTD: 10 mg/kg/day**

For both adults and children

(French Health Products Safety Agency, 2011)

Uncertainty Factors?

Global UF = 810

$$TRV_{MTD} = \frac{10}{810}$$

$$= 12.3 \times 10^{-3} \text{ mg/kg/day}$$

$TRV_{MTD} = 12.3 \times 10^{3}$ ng/kg/day

$UF_L = 3$

LOAEL-to-NOAEL

$UF_S = 3$

Short-term to long-term exposure

$UF_A = 1$

Animal to Human

$UF_H = 3$

Average Human to Sensitive Human

$UF_D = 3$

Database Insufficiency

$MF = 10$

Modifying Factor

HEALTH RISK ASSESSMENT BY TOXICOLOGICAL APPROACH BASED ON MTD

DWEL ?
adults

DWEL ?
children

MOE ?
adults

MOE ?
children

HEALTH RISK ASSESSMENT BY TOXICOLOGICAL APPROACH BASED ON MTD

$$\text{DWEL}_{\text{adults}} = \frac{TRV_{tox} \times BW}{IR} = \frac{12.3 \times 10^3 \times 60}{2} = \frac{(ng/kg/day) \times kg}{L/day} = 369 \times 10^3 \text{ ng / L}$$

$$\text{DWEL}_{\text{children}} = \frac{TRV_{tox} \times BW}{IR} = \frac{12.3 \times 10^3 \times 16{,}7}{1} = \frac{(ng/kg/day) \times kg}{L/day} = 206 \times 10^3 \text{ ng / L}$$

MOE ?
adults

MOE ?
children

HEALTH RISK ASSESSMENT BY TOXICOLOGICAL APPROACH BASED ON MTD

$$\text{DWEL}_{\text{adults}} = \frac{TRV_{tox} \times BW}{IR} = \frac{12.3 \times 10^3 \times 60}{2} = \frac{(ng/kg/day) \times kg}{L/day} = 369 \times 10^3 \text{ ng / L}$$

$$\text{DWEL}_{\text{children}} = \frac{TRV_{tox} \times BW}{IR} = \frac{12.3 \times 10^3 \times 16{,}7}{1} = \frac{(ng/kg/day) \times kg}{L/day} = 206 \times 10^3 \text{ ng / L}$$

$$\text{MOE}_{\text{adults}} = \frac{\text{DWEL adult}}{C_{CBZ}} = \frac{369{,}000}{33} = \frac{ng/L}{ng/L} = 11{,}182$$

$$\text{MOE}_{\text{children}} = \frac{\text{DWEL children}}{C_{CBZ}} = \frac{206{,}000}{33} = \frac{(ng/kg/day) \times kg}{L/day} = 6243$$

MOE calculated from DWEL and carbamazepine (CBZ) concentration found in WICH following the derivation of the TRV toxicological approach using the MTD approach

	Methods	DWEL (ng/L)		Margins of exposure (MOE)	
		Adults	Children	Adults	Children
Measured concentration of carbamazepine in WHC = 33 ng/L	Toxicity reference value based on minimum therapeutic dose (TRV_{MTD})	369,000	206,000	11,182	6243

HEALTH RISK ASSESSMENT BY TOXICOLOGICAL APPROACH BASED ON TTC

DWEL ?
adults

DWEL ?
children

MOE ?
adults

MOE ?
children

TTC = 2.5 x 10^{-3} µg/kg/day

A person corresponds to an adult of 60 kg

TTC IS A CONSERVATIVE APPROACH

TTC = 2.5 ng/kg/day

TRV_{Tox} = 3300 ng/kg/day

TRV_{RTD} = 12,300 ng/kg/day

(3) TTC

The Threshold of Toxicological Concern (TTC) approach?

Calculated value?

0.15 µg/person/day (excess risk of 10^{-6})
human exposure dose below which the risk is believed to be sufficiently low to exempt a substance from toxicological investigations
Probabilistic approach based on the concept of structural similarity

Data used?

built from a database of known carcinogenic substances

Limits?

Only dedicated to substances for which there is no available data, but allows to be freed from the marketing authorization dossier and cover the uncertainties related to the carcinogenic properties

HEALTH RISK ASSESSMENT BY TOXICOLOGICAL APPROACH BASED ON TTC

$$\text{DWEL}_{\text{adults}} = \frac{\text{TTC x BW}}{\text{IR}} = \frac{2.5 \times 60}{2} = \frac{\text{(ng/kg/day) x kg}}{\text{L/day}} = 75 \text{ ng / L}$$

$$\text{DWEL}_{\text{children}} = \frac{\text{TTC x BW}}{\text{IR}} = \frac{2.5 \times 16{,}7}{1} = \frac{\text{(ng/kg/day) x kg}}{\text{L/day}} = 41.7 \text{ ng / L}$$

MOE ?
adults

MOE ?
children

HEALTH RISK ASSESSMENT BY TOXICOLOGICAL APPROACH BASED ON TTC

$$\text{DWEL}_{\text{adults}} = \frac{\text{TTC x BW}}{\text{IR}} = \frac{2.5 \times 60}{2} = \frac{\text{(ng/kg/day) x kg}}{\text{L/day}} = 75 \text{ ng / L}$$

$$\text{DWEL}_{\text{children}} = \frac{\text{TTC x BW}}{\text{IR}} = \frac{2.5 \times 16{,}7}{1} = \frac{\text{(ng/kg/day) x kg}}{\text{L/day}} = 41.7 \text{ ng / L}$$

$$\text{MOE}_{\text{adults}} = \frac{\text{DWEL adult}}{C_{CBZ}} = \frac{75}{33} = \frac{\text{ng/L}}{\text{ng/L}} = 2.3$$

$$\text{MOE}_{\text{children}} = \frac{\text{DWEL children}}{C_{CBZ}} = \frac{41.7}{33} = \frac{\text{(ng/kg/day) x kg}}{\text{L/day}} = 1.3$$

MOE calculated from DWEL and carbamazepine (CBZ) concentration found in WICH following the TTC approach

	Methods	DWEL (ng/L)		Margins of exposure (MOE)	
		Adults	Children	Adults	Children
Measured concentration of carbamazepine in WIHC = 33 ng/L					
	Threshold of toxicological concern (TTC)	75	41.7	2.3	1.3

HEALTH RISK ASSESSMENT BY TOXICOLOGICAL APPROACH BASED ON TTC

HRA for the metabolite EP-CBZ?

HEALTH RISK ASSESSMENT BY TOXICOLOGICAL APPROACH BASED ON TTC

$$\text{DWEL}_{\text{adults}} = \frac{\text{TTC} \times \text{BW}}{\text{IR}} = \frac{2.5 \times 60}{2} = \frac{(\text{ng/kg/day}) \times \text{kg}}{\text{L/day}} = 75 \text{ ng / L}$$

$$\text{DWEL}_{\text{children}} = \frac{\text{TTC} \times \text{BW}}{\text{IR}} = \frac{2.5 \times 16{,}7}{1} = \frac{(\text{ng/kg/day}) \times \text{kg}}{\text{L/day}} = 41.7 \text{ ng / L}$$

$$\text{MOE}_{\text{Adults}} = \frac{\text{DWEL adult}}{C_{CBZ}} = \frac{75}{6} = \frac{\text{ng/L}}{\text{ng/L}} = 12.5$$

$$\text{MOE}_{\text{children}} = \frac{\text{DWEL children}}{C_{CBZ}} = \frac{41.7}{6} = \frac{(\text{ng/kg/day}) \times \text{kg}}{\text{L/day}} = 7$$

MOE calculated from DWEL and 10,11-epoxycarbamazepine (EP-CBZ) concentration found in WICH following the TTC approach

	Methods	DWEL (ng/L)		Margins of exposure (MOE)	
		Adults	Children	Adults	Children
Measured concentration of 10,11-epoxycarbamazepine in WIHC = 6 ng/L	Threshold of toxicological concern (TTC)	75	41.7	12.5	7

DISCUSSION AND CONCLUSIONS

- The TRV_{Tox} approach should be retained as long as the marketing authorization dossier data are available. A derivation of the TRV_{Tox} approach involving the use of MTD may be used as a point of departure if the toxicological data are missing. However, it cannot be generalised to substances such cytotoxic agents, allergens, antibiotics, hormones and metabolites. The TTC approach can only be used in last line and must be reserved to substances for which there is no available data e.g. for certain metabolites.

- For all approaches used, the MOE indicate that there is no appreciable risk to human health exposure to carbamazepine and its major metabolite.

- The exposure scenarios should take into account the cumulative amounts of these chemicals via both WIHC and fish consumption for a more relevant health hazard evaluation.

- The authors underline the importance of testing the effects of mixtures of pharmaceuticals because drug residues often occur as mixtures and not as single contaminants after entering wastewaters.