

# Incorporating the Threshold of Toxicological Concern into Regulatory Decisions under the Toxic Substances Control Act (TSCA)

Todd Stedeford

Office of Chemical Safety and Pollution Prevention, US EPA

*Disclaimer: The views expressed in this presentation are those of the presenter and do not represent Agency policy or endorsement. Mention of trade names of commercial products should not be interpreted as an endorsement by the U.S. Environmental Protection Agency.*



# Topics Covered

- TSCA Sections 5 (new chemical substances) and 6 (existing chemical substances)
- TSCA Section 4 (h) – Reduction of Testing on Vertebrates
- Threshold of Toxicological Concern (TTC)
  - Background and regulatory applications
  - Potential applications under TSCA



# Toxic Substances Control Act (TSCA)

New Chemical Substances (NCS)

Determination that the NCS:

1. "presents",<sup>1</sup>
2. "information is insufficient",<sup>2</sup>
3. "may present",<sup>3</sup>
4. "substantial quantities" or "significant or substantial exposure",<sup>4</sup> or
5. "not likely to present"<sup>5</sup>

"an unreasonable risk of injury to health or the environment"

Existing Chemical Substances (ECS)

Prioritization of the ECS as:<sup>6</sup>

1. "low-priority substance", or
2. "high-priority substance" (HPS)

Risk evaluation on HPS and determination whether it presents:<sup>7</sup>

"an unreasonable risk of injury to health or the environment"



# Review of New and Existing Chemical Substances at EPA

- Risk-based determinations/evaluations must be based on:
  - The best available science,
  - The weight of the scientific evidence, and
  - “Without consideration of costs or other non-risk factors”
- EPA assesses a wide variety of potential human health and environmental effects associated with the known, intended, and reasonably foreseeable conditions of use for new and existing chemical substances.



# Types of Data Utilized for New and Existing Chemical Substance Reviews

- New chemical substances
  - Submitters must provide all data in their possession or control related to health and environmental effects
  - EPA may require the development of new information relating to the new chemical substance
- Existing chemical substances
  - EPA must first take into account reasonably available existing information
  - EPA may then require the development of new information relating to the existing chemical substance



# TSCA Chemical Hazard Assessment: Approach

- Data Preference: Chemical-specific test data > Analogue data > Modeled data
- Analogue Data: EPA Considers:
  - Physical-chemical properties (*e.g.*, log  $K_{ow}$ , water solubility, and melting point), presence and position of reactive functional groups, *etc.*
  - Potential metabolites or degradates (*e.g.*, hydrolysis products)
  - TSCA New Chemicals Program (NCP) Chemical Categories
  - Structural alerts for toxicity
  - Identify hazards associated with the category and/or structural alerts
- What if the “information are insufficient” for making a risk determination?



# Statutory Mandate: TSCA Section 4(h)(1)

- Prior to requesting testing using vertebrates:
  - Consider *reasonably available existing information*, and
  - Encourage and facilitate (Section 4(h)(1)(B)(I, ii and iii):
    - “Scientifically valid test methods and strategies that reduce or replace use of vertebrate animals while providing information of equivalent or better scientific quality and relevance that will support regulatory decisions;”



# Threshold of Toxicological Concern (TTC)\*

- EFSA and WHO (2016) identified the threshold of toxicological concern (TTC) approach as a “pragmatic, scientifically valid methodology to assess the safety of substances of unknown toxicity found in food”<sup>1</sup>
- What is a TTC?
  - “A level of exposure that is considered to be of no appreciable risk to human health despite the absence of chemical-specific toxicity data” (Patlewicz *et al.*, 2018)<sup>2</sup>

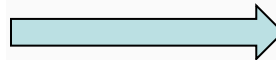
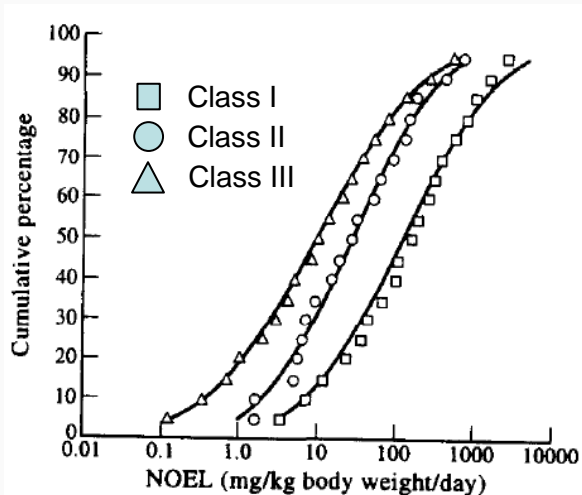
\*For background, see: Grace Patlewicz (2016) Threshold of Toxicological Concern Approach in Regulatory Decision-Making: The Past, Present, and Future, U.S. EPA, available at:

<https://www.toxicology.org/events/shm/fda/docs/2%20Patlewicz%20SOT%20FDA%20Cramer.pdf>



# Threshold of Toxicological Concern (TTC)...cont.

- The non-cancer TTC approach utilizes the classification scheme originally proposed by Cramer *et al.* (1978)<sup>1</sup> that consists of a series of 33 questions that lead to a final classification of low (Class I), moderate (Class II), or serious (Class III) toxicity.
- Munro *et al.* (1996)<sup>2</sup> evaluated a database of 613 chemicals, classified the chemicals according to the Cramer classes, calculated the cumulative distribution of NOELs for each, and derived thresholds of acceptable human exposure.



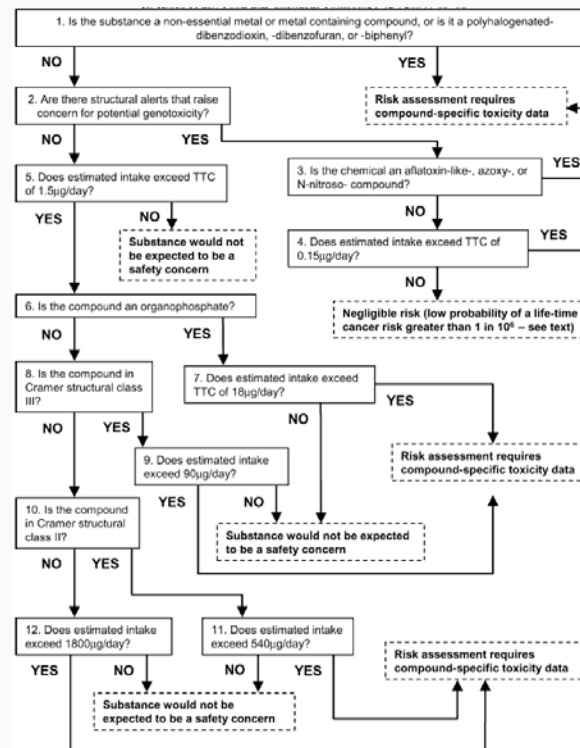
Cramer class	5 <sup>th</sup> percentile NOEL (mg/kg-bw/day)	Human exposure threshold (mg/day) <sup>a</sup>
I	3.0	1.8
II	0.91	0.54
III	0.15	0.09

<sup>a</sup> Calculated by multiplying 5<sup>th</sup> percentile NOEL by 60 kg and dividing by a safety factor 100.



# Threshold of Toxicological Concern (TTC)...cont.

- Kroes *et al.* (2004)<sup>1</sup> proposed a decision-tree that incorporates different TTCs to different structural characteristics





# Threshold of Toxicological Concern (TTC)\*

- The TTC is a tool that may be used to justify waiving of generation of animal data and is regarded as an extension of read-across and chemical category approaches (ECHA, 2017)<sup>1</sup>
- Used by regulatory agencies, e.g., FDA (food-contact articles)<sup>2</sup> and EFSA (food safety assessment)<sup>3</sup> when considering very low-level lifetime oral exposures



# Threshold of Toxicological Concern (TTC)...cont.

- In 1995, FDA implemented a threshold of regulation (ToR) value of 1.5  $\mu\text{g}/\text{person}/\text{day}$  for food contact materials.<sup>1</sup>
- ToR applies to substances that migrate or are expected to migrate into food and are exempted from regulation as food additives at levels below the ToR if:<sup>2</sup>
  - The substance has not been shown to be a carcinogen in humans or animals, and there is no reason, based on structure, to suspect the substance is a carcinogen;
  - The substance does not contain a carcinogenic impurity. If it does, it must not have a  $\text{TD}_{50}$  value less than 6.25  $\text{mg}/\text{kg}\text{-bw}/\text{day}$ ;
  - The substance presents no other health and safety concerns because exposures  $\leq 1.5 \mu\text{g}/\text{person}/\text{day}$  or substance currently regulated for direct addition to food and exposure from proposed use is  $\leq 1\%$  of the ADI;
  - The substance has no technical effect in or on the food to which it migrates; and
  - The substance use has no significant adverse impact on the environment.



# Threshold of Toxicological Concern (TTC)...cont.

- The research by Munro *et al.* (1996), Kroes *et al.* (2004), EFSA (2012), and others led to the following TTC values used by EFSA<sup>1</sup>

TTC Values - classification		
Classification	TTC value in $\mu\text{g}/\text{person}$ per day <sup>a</sup>	TTC value in $\mu\text{g}/\text{kg-bw}$ per day
Potential DNA-reactive mutagens and/or carcinogens	0.15	0.0025
Organophosphates and carbamates	18	0.3
Cramer Class III	90	1.5
Cramer Class II	540	9.0
Cramer Class I	1,800	30

<sup>a</sup> Calculated based on a body weight value of 60 kg.

- Note: The overall workflow and datasets for the Cramer classes are not the same as the datasets used for substances with genotoxicity alerts nor for organophosphates/carbamates.



# Threshold of Toxicological Concern (TTC)...cont.

- EFSA identified the following substances as not suitable for the TTC approach<sup>1</sup>
  - Those covered by regulations that require the submission of toxicity data;
  - Those with data that allow for a risk assessment;
  - Those which are not represented in the database or are outside the domain of applicability (e.g., inorganic substances);
  - Those with special properties:
    - High potency carcinogens (e.g., aflatoxin-like)
    - Steroids
    - Substances with a potential for bioaccumulation (e.g., polyhalogenated dibenzodioxins)



# Threshold of Toxicological Concern (TTC)...cont.

- The TTC approach is well-established for oral exposures; however, TTCs have been proposed for inhalation exposures,<sup>1,2,3</sup> route-to-route extrapolations,<sup>4</sup> other endpoints (e.g., skin sensitization),<sup>5</sup> and for ecotoxicity<sup>6</sup>
- Has the TTC approach been considered for regulatory decisions on industrial chemicals?
- Yes, several have considered the TTC approach for industrial chemicals (e.g., Health Canada, ECHA, and EPA).

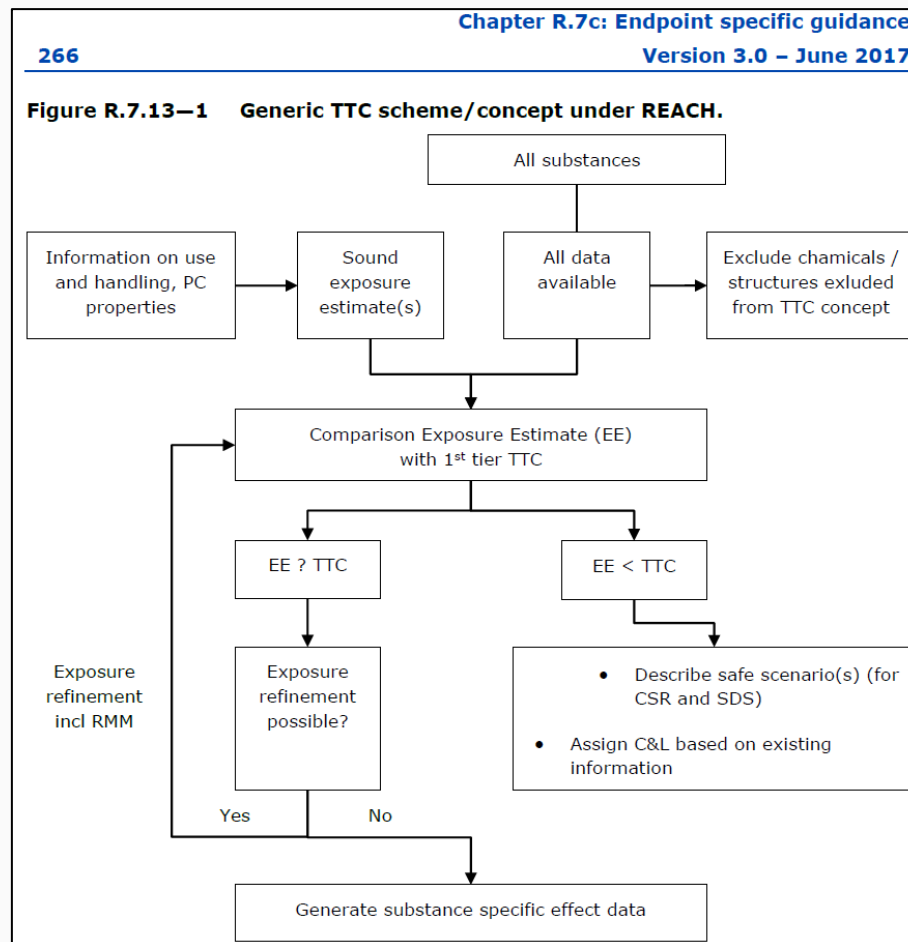


# Incorporating TTC Approaches for Commercial Chemicals

- Health Canada (2016) identified 89 substances from its list of priority substances, which were unlikely to pose a risk to human health using a TTC-based approach and current exposure levels<sup>1</sup>
- ECHA (2017) discussed different TTC approaches, their limitations, criteria for use, and their potential use under REACH<sup>2</sup>
- ECHA (2017) provided a generic TTC scheme that illustrates the way a TTC may be used and would precede any substance-specific testing



# Incorporating TTC Approaches for Commercial Chemicals





# Incorporating TTC Approaches for Commercial Chemicals

- EPA's (2018) draft strategic plan identified the TTC approach as one for possible evaluation for its utility with “priority setting; expansion of existing new chemical categories; and identification of new categories for [the] new chemical categories document.”<sup>1</sup>
- EPA's (2018) response to comments on the draft strategic plan stated:<sup>2</sup>

“EPA believes that exploration and potential implementation of the toxicological threshold of concern approach, at least for some chemical structural classes, is an important possible avenue for making some TSCA decisions. EPA is considering this topic as part of collaborative efforts...”
- This collaboration was initiated in 2020 by external stakeholders with EPA and other groups with the intent of exploring potential TTC applications under TSCA.



# Existing “TTC-like” Approaches for New Chemical Substances under TSCA

- EPA implemented a “TTC-like” approach as an exemption for some new chemical substances, regardless of production volume
- In 1995, EPA added a new exemption category for new chemical substances with low environmental releases and low human exposures known as the “low release and exposure (LoREX) exemption”.<sup>1</sup>
  - Exemption developed based on EPA’s experience conducting risk assessments on over 25,000 new chemical substances up to that time



# Existing “TTC-like” Approaches for New Chemical Substances under TSCA

- ***Environmental releases:***
  - Surface water: prevent direct/indirect releases (limit of 1 ppb)
  - Ambient air: maximum annual average concentration from incineration is 1  $\mu\text{g}/\text{m}^3$
  - Land/groundwater: no landfill or other land disposal methods, unless substance will not migrate to groundwater
  - Fugitive air: unrelated to incineration, no generic eligibility criteria established, but EPA noted that emissions under 23 kg/site/year were seldom found to present an unreasonable risk
- ***Human exposures:***
  - Workers: no dermal/inhalation exposures using adequate controls, work practices, and/or personal protective equipment
  - Consumers/general population: no exposures, except as stated above
- Upon approval of a LoREX exemption, the uses and exposure/release controls are binding, as are listed manufacturing sites, unless specific conditions are met



# Existing “TTC-like” Approaches for New Chemical Substances...cont.

- EPA excluded new chemical substances with possible consumer and general population exposures from the LoREX exemption
- Excluded because EPA could not develop meaningful exposure criteria that would consistently screen out those substances which may present unreasonable risks due to the wide range of possible exposures<sup>1</sup>
- New chemical substances with intended consumer uses (e.g., paints, detergents, dyes, etc.) would have to be submitted as premanufacture notices (PMNs) or under another PMN exemption (e.g., low volume exemption or LVE)<sup>2</sup>



# Opportunities to Incorporate the TTC Approach for New Chemical Substances under TSCA

- In 1995, EPA implemented an exemption for new chemical substances manufactured at 10,000 kg or less per year (*i.e.*, LVEs)<sup>1</sup>
- LVE substances, including reasonably anticipated metabolites, environmental transformation products, byproducts, or impurities, will not be approved if they raise serious acute/chronic health effects or significant environmental effects<sup>2</sup>
- Proposed controls for exposure/release are binding on the manufacturers, as are the uses and manufacturing sites, unless specific conditions are met<sup>3</sup>
- LVEs are only approved if EPA affirmatively finds that the manufacture, processing, distribution in commerce, use, and disposal will not present an unreasonable risk to human health or the environment<sup>4</sup>



## Opportunities to Incorporate the TTC Approach for New Chemical Substances under TSCA...cont.

- For new chemical substance notifications (*e.g.*, PMNs), EPA and/or submitters generally identify chemical analogues for informing risk assessments
- When no suitable analogues are available, the TTC approach may be used by submitters to identify, for example, opportunities for exposure/release reduction through engineering controls, workplace practices, and/or personal protective equipment prior to submitting a PMN
- EPA encourages submitters to consult with EPA prior to doing so. Pre-submission meeting information is here: <https://www.epa.gov/reviewing-new-chemicals-under-toxic-substances-control-act-tsca/filing-pre-manufacture-notice-epa>



# Opportunities to Incorporate the TTC Approach for Existing Chemical Substances under TSCA

- Under Section 6 of TSCA and the implementing regulations, EPA is required to screen existing chemical substances against the following criteria:<sup>1</sup>
  - Hazard and exposure potential;
  - Persistence and bioaccumulation;
  - Potentially exposed or susceptible populations;
  - Storage near significant sources of drinking water;
  - Conditions of use or significant changes in conditions of use;
  - Production volume or significant changes in production volume; and
  - Other risk-based criteria
- Based on the results of the screening, EPA proposes to designate a substance as either a high-priority substance or a low-priority substance<sup>2</sup>
- EPA considers additional information collected from the proposal and publishes a final designation for each substance<sup>3</sup>





# Opportunities to Incorporate the TTC Approach for Existing Chemical Substances under TSCA...cont.

- Patlewicz *et al.* (2018)<sup>1</sup> used the TTC approach with chemical specific high throughput exposure estimates (HTE), as developed by Wambaugh *et al.* (2014)<sup>2</sup>, to prioritize thousands of substances
- The results indicated that the HTE:TTC approach could be adopted as a pragmatic first step in risk-based prioritization of thousands of chemicals

TTC category	Number of chemicals	TTC (µg/kg-day for 60 kg adult)	Percentage of Substances Exceeding the TTC	
			UCI Exposure Value (number of chemicals)	Median Exposure Value (number of chemicals)
<b>Cramer class III</b>	3214	1.5 µg/kg-day	2% (58)	0
<b>Cramer class II</b>	332	9.0 µg/kg-day	0	0
<b>Cramer class I</b>	1294	30 µg/kg-day	0	0
<b>AChEIs</b>	102	0.3 µg/kg-day	1% (1)	0
<b>Genotoxic alerts</b>	1853	Kroes 0.0025 µg/kg-day	94% (1740)	4% (79)
		ICH 0.025 µg/kg-day	18% (333)	1% (19)



# Conclusions

- The TTC approach represents a possible tool for screening some structural classes of new and existing chemical substances to make preliminary decisions on new and existing chemical substances, for example:
  - for evaluating exposure/release controls for new chemical substances and identifying the need for possible refinements, in the absence of chemical-specific or analogue data,
  - for risk-based prioritization of existing chemical substances,
  - as a non-animal approach for making initial decisions regarding the need for further data gathering
- Several points warrant further evaluation, including:
  - Oral TTC values are well established; however, TSCA risk assessments may include evaluations *via* other routes (e.g., dermal and inhalation), other endpoints (e.g., portal of entry effects), less than lifetime assessments, and ecological assessments



# Conclusions

- Progress continues to be made:
  - Proposed inhalation TTC values (*e.g.*, Nelms and Patlewicz, 2020, in press)<sup>1</sup>
  - ecoTTCs and subcategorization into “MOA-like” categories (*e.g.*, HESI project)<sup>2</sup>
  - Refinements to the organophosphate and carbamates alerts (*e.g.*, Nelms *et al.*, 2019)<sup>3</sup>
  - Internal TTCs (*e.g.*, Ellison *et al.*, 2019)<sup>4</sup>
  - Online resources (*e.g.*, ScitoVation’s TTC Data Mart; Nicolas *et al.*, 2020)<sup>5,6</sup>



## Acknowledgements

- Tala Henry, EPA/OPPT
- Louis “Gino” Scarano, EPA/OPPT/NCD
- Iris Camacho, EPA/OPPT/NCD
- Grace Patlewicz, EPA/ORD/CCTE/CCED/CCCB
- Rick Becker, ACC

**THANK YOU!**

**QUESTIONS?**

