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Updates to Biopesticide Regulation in Canada

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Outline

- New Requirements for Companion Animal Safety Testing
- Essential Oil-based Products
- Integrated Approaches to Testing and Assessment
- RNA Interference in Pest Control Products
- Ongoing Challenges with Submissions

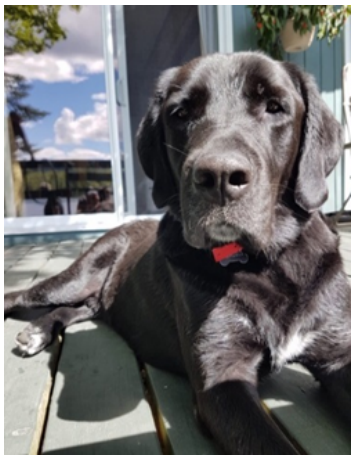
Pesticides Used on Companion Animals

- Revisions to toxicology data requirements for all products under USC 24 (Companion Animals)
  - Spot-on products
  - Shampoos
  - Spray repellents
  - Powders
  - Collars

- Revisions based on:
  - Number of incident reports received for flea and tick products
  - Effects seen in the Companion Animal Safety Study (CAS; DACO 4.6.9) were not always consistent with those reported in incident reports

Pesticides Used on Companion Animals cont'd

- New requirement in addition to CAS: Clinical Safety Study
  - Larger group sizes, more diverse test group representative of target population
  - Provides evaluation of potential adverse effects at label dose under actual use conditions
  - Designed to include assessment of efficacy
- Applicants encouraged to engage in presubmission consultation process prior to initiation of studies



Revisions to Data Requirements for Pesticide Products Used on Companion Animals:
https://www.canada.ca/en/health-canada/services/consumer-product-safety/reports-publications/pesticides-pest-management/policies-guidelines/revisions-data-requirements-pesticide-products-companion-animals.html

Essential Oil-based Products

- Essential Oil-based Personal Insect Repellents (EOPIR) Information Requirements for Assessment of Risks to Human Health Regulatory Directive 2017-02
  - Specific to human health requirements for EOPIRs, as well as:
    - Other uses under USC 26 (Human Skin, Clothing and Proximal Sites): Any EO-based product used on soft furnishings, bedding, clothing
    - Uses under USC 24 (Companion Animals): EO-based products applied directly to domestic animals

- Key changes:
  - Replace technical grade active ingredient Tier I requirements for separate short-term and developmental toxicity studies with a **combined repeated dose/reproductive/developmental study** (OECD TG 422)
  - Include **dermal absorption** (*in vitro*) as a Tier I data requirement for EOPIRs
  - **Eliminate Tier III** information requirements; instead re-profile EOPIR as conventional chemical pesticide with associated data requirements

Regulatory Directive 2017-02:

http://www.hc-sc.gc.ca/cps-spc/pubs/pest/_pol-guide/dir2017-02/index-eng.php

Essential Oil-based Products cont'd

Methyleugenol

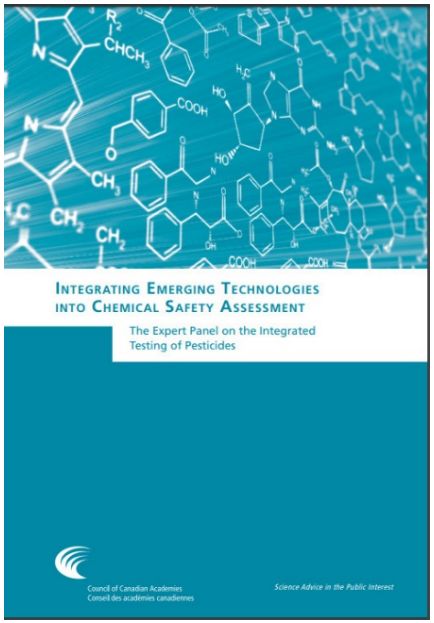
- Essential oils from certain sources may contain methyleugenol, a genotoxic carcinogen
  - PMRA limit for EO-based end-use products (EPs) in USC 26 and 24 < 0.0002% (2 ppm)
  - Applicants must provide analyses to show EOPIRs meet the limit
  - Methyleugenol analysis must also be performed for EO-based products for food uses
    - No limit, however level will be incorporated into risk assessment

Heavy metals

- Heavy metal concentrations in end-use products in USC 26 and 24 must meet the following limits: Hg 1 ppm; As 3 ppm; Cd 3 ppm; Sb 5 ppm; Pb 10 ppm
  - Testing waived for oils demonstrated to be Food Chemicals Codex Grade or Food Grade Edible
  - Analysis must be conducted for food use EPs, and levels will be used in risk assessment

Integrated Approaches to Testing and Assessment (IATA)

- PMRA is committed to the 3Rs (reduce, refine, and replace animal testing) wherever possible
- Success has relied on multistakeholder collaboration
  - Being engaged with industry, other regulatory authorities, research community
- Design thinking approach
  - Strong understanding of traditional approaches required to be able to inform new methods



IATA Cont'd

- New Approach Methodologies (NAMs) not immediately envisioned to be replacement tools, but rather to refine what is seen *in vivo*
  - AOPs, importance of covering biological space
  - Need to build confidence in new methods
    - Alternative organisms
    - Genomics
    - High throughput

IATA Cont'd

- Acute Dermal Toxicity Study Waiver (Science Policy Note 2017-03)
  - https://www.canada.ca/content/dam/hc-sc/documents/services/consumer-product-safety/reports-publications/pesticides-pest-management/policies-guidelines/science-policy-notes/2017/acute-dermal-toxicity-waiver-spn2017-03-eng.pdf
- Guidance for Waiving or Bridging of Mammalian Acute Toxicity Tests for Pesticides
  - https://www.canada.ca/content/dam/hc-sc/migration/hc-sc/cps-spc/alt_formats/pdf/pubs/pest/pol-guide/toxicity-guide-toxicite/toxicity-guide-toxicite.eng.pdf
- Defined Approaches for Skin Sensitization
  - EPA Interim Science Policy: https://www.scc-gmbh.de/images/scc/Downloads/EPA-HQ-OPP-2016-0093-0090.pdf

IATA cont'd

- *In silico* models (e.g. (Q)SAR analyses) used as supporting information and in weight of evidence approach for data poor components
  - Metabolites, formulants
  - https://www.canada.ca/en/health-canada/services/consumer-product-safety/pesticides-pest-management/public/international/north-american-free-trade-agreement-technical-working-group/quantitative-structure-activity-relationships-guidance-document.html

- Please refer to Annex 1 for PMRA's IATA Road Map

RNA Interference (RNAi) in Pest Control Products

- Unique challenges of regulating RNAi
  - Mode of action of RNAi is sequence-specific due to requirement for complementary base-pairing with mRNA target
  - Exposure estimates (potential for environmental uptake and amplification (i.e. environmental and systemic RNAi), differences in RNAi machinery across taxa, stability, formulants, etc.)
- No regulatory precedent for exogenously-applied RNAi-based products
  - A new regulatory framework is being developed for this new class of dsRNA pesticides
  - OECD Expert Working Group has completed draft document on environmental considerations; aiming to publish late 2020
- Data requirements determined on a case by case basis
  - Pre-submission consultation required
  - Research authorizations required for any research conducted outside of laboratory

Avoiding Pitfalls

Ongoing challenges/issues

- No pre-submission consultation
  - Currently a free service to obtain guidance on data requirements and options to address them
  - Recommended for all biopesticides
  - Guidance is valid for two years
  - Potential cost savings

Ongoing challenges/issues cont'd

- Data dumping
  - Clearly indicate which DACO number(s) apply to each document
  - Submit all referenced published studies/papers separately

- Formulation ingredients
  - Avoid formulants of health or environmental concern and primary human allergens
  - Characterize any impurities present

Formulant search:
https://open.canada.ca/data/en/dataset/ededff77-a021-48d6-89a5-cdbcd75fb4ff

Ongoing challenges/issues

- Waiver rationales
  - Support rationales with copies of published literature; full text studies required
  - Acute toxicity data cannot satisfy requirement for repeated dose studies by relevant route(s) of exposure
  - Generally, GRAS status, USEPA status, use in cosmetics or other consumer products and “all-natural” claims are not sufficient
    - If relying on registration status in another jurisdiction, registration dossier must be provided to PMRA to allow independent review
  - If providing information on a surrogate compound, toxicological equivalence with proposed active ingredient must be demonstrated
    - Structural similarity is not a sufficient justification for use of a surrogate
    - If using (Q)SAR predictions to support, provide sufficient details on program inputs

Ongoing challenges/issues cont'd

- Waiver rationales cont'd
  - If utilizing a 'major component' approach (e.g. essential oil or other multi-component active), provide composition data on TGAI, and rationale as to why major component is an appropriate surrogate
  - Avoid waivers relying largely on lack of exposure, as hazards must be identified
  - Avoid submitting rationales for all human health or all environmental toxicology studies

Ongoing challenges/issues cont'd

- Toxicology and Environnmental tox studies
  - Justify any deviations from guidelines
  - Additional information (possibly including higher tier studies) may be required if the available information is inadequate or if risks are identified in Tier 1 studies
  - Be prepared that mitigative measures and hazard statements may be required

- Residue data for products used on food crops
  - Must demonstrate that any anticipated residues of the parent compound or metabolites will not pose a toxicological concern
  - Crop residue data may be required if residues of toxicological concern in excess of natural background levels are likely to occur on a consumable commodity

Ongoing challenges/issues cont'd

- Identification of secondary metabolites of concern for microbial pest control agents
  - Discussion on identified metabolites (i.e. toxicity profile, targets, closely related microorganisms, etc.)
  - Determine whether secondary metabolites are present in TGAI, EP produced according to proposed manufacturing methods
    - Include positive control (known producer of secondary metabolite)
    - Testing in the edible portion of plants may be required if metabolite is produced post-application
- Part M4 toxicity tests should be conducted with TGAI as some formulants may bind to metabolites

http://www.oecd.org/officialdocuments/publicdisplaydocumentpdf/?cote=env/jm/mono(2018)33&doclanguage=en

http://www.oecd.org/officialdocuments/publicdisplaydocumentpdf/?cote=env/jm/mono(2018)33/ann1&doclanguage=en

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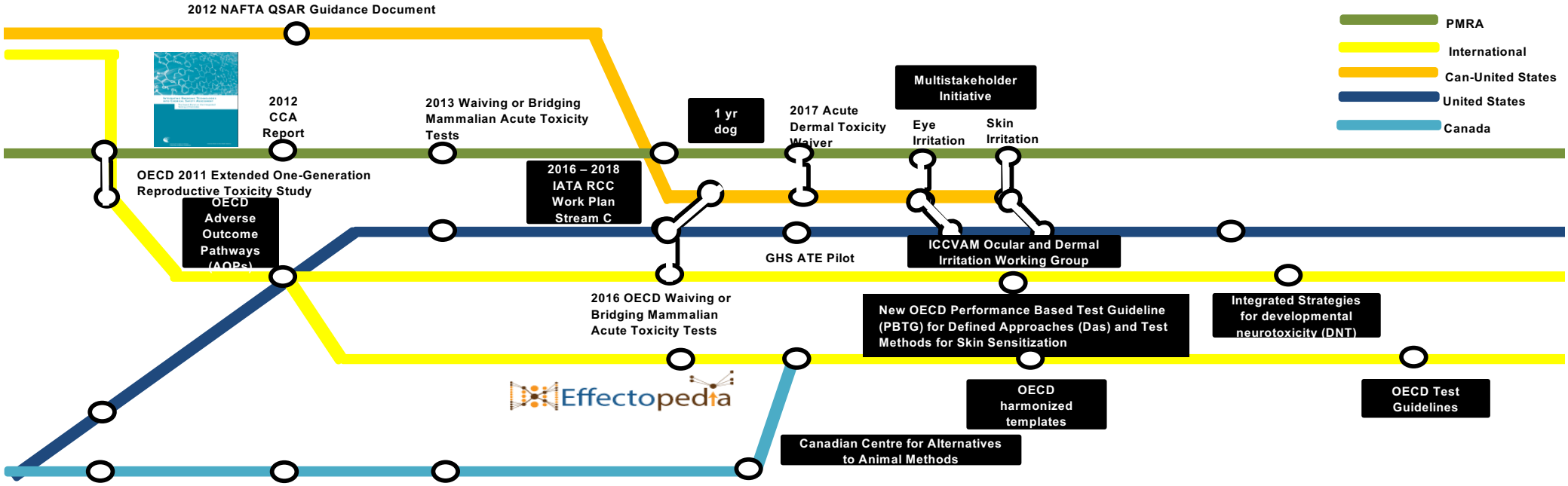
Questions?

Comments?

Annex 1
PMRA IATA Road Map



F. Bailey 2019