# Use of new approach methodologies to meet pesticide testing requirements in India

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Central Insecticides Board & Registration Committee

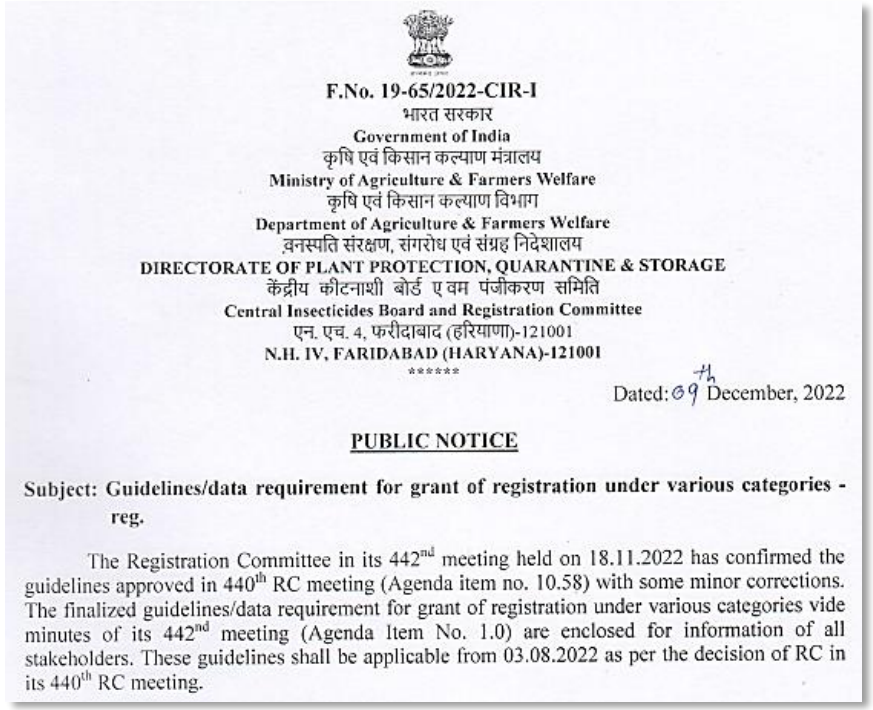
**'Webinar series on the use of new approach methodologies for the risk assessment of pesticides'**

10 March, 2023

# Overview

- Acceptance of non-animal approaches in the new guidelines for pesticide toxicity testing
  - *In chemico/In vitro/ex vivo/in silico* methods
  - Integrated approaches to testing and assessment
  - Weight-of-evidence approach
  - Read-across/data bridging
  - Adverse outcome pathways
- Opportunities to waive tests on animals
- Relevant guidance documents from scientific organisations
- Other toxicity data requirements
- General benefits of using new approach methodologies
- Additional considerations for pesticide registration

# Acceptance of non-animal approaches



F.No. 19-65/2022-CIR-I
भारत सरकार
Government of India
कृषि एवं किसान कल्याण मंत्रालय
Ministry of Agriculture & Farmers Welfare
कृषि एवं किसान कल्याण विभाग
Department of Agriculture & Farmers Welfare
वनस्पति संरक्षण, संगरोध एवं संग्रह निदेशालय
DIRECTORATE OF PLANT PROTECTION, QUARANTINE & STORAGE
केंद्रीय कीटनाशी बोर्ड एवम पंजीकरण समिति
Central Insecticides Board and Registration Committee
एन. एच. 4, फरीदाबाद (हरियाणा)-121001
N.H. IV, FARIDABAD (HARYANA)-121001
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Dated: 09th December, 2022

PUBLIC NOTICE

Subject: Guidelines/data requirement for grant of registration under various categories - reg.

The Registration Committee in its 442nd meeting held on 18.11.2022 has confirmed the guidelines approved in 440th RC meeting (Agenda item no. 10.58) with some minor corrections. The finalized guidelines/data requirement for grant of registration under various categories vide minutes of its 442nd meeting (Agenda Item No. 1.0) are enclosed for information of all stakeholders. These guidelines shall be applicable from 03.08.2022 as per the decision of RC in its 440th RC meeting.

**Note: The general recommendations as mentioned in the Guidance Document on Toxicology for registration of Chemical Pesticides in India will be applicable on the basis of merit case to case basis.**

**Waiver would be considered only when existing information provides robust and full scientifically sound weight of evidence approach and read across/bridging from structurally and /or biologically related similar pesticides specifically case to case basis on full merits.**
**The replacement alternatives not involving experiments on animals would not be normally considered,except in exceptional and rare cases where in case of alternatives if available with full and sound justification is provided specifically case to case basis on merit subject to full satisfaction of the expert regarding full toxicity data provided for the alternatives.**

https://ppqs.gov.in/sites/default/files/public_notice_merged_1.pdf

- **Non-animal methods should be used when scientifically justified**
- **Applicable to both chemical pesticides and bio-pesticides (botanicals, microbials and semiochemicals/pheromones)**

# Acceptance of non-animal approaches

**Note: The general recommendations as mentioned in the Guidance Document on Toxicology for registration of Chemical Pesticides in India will be applicable on the basis of merit case to case basis.**

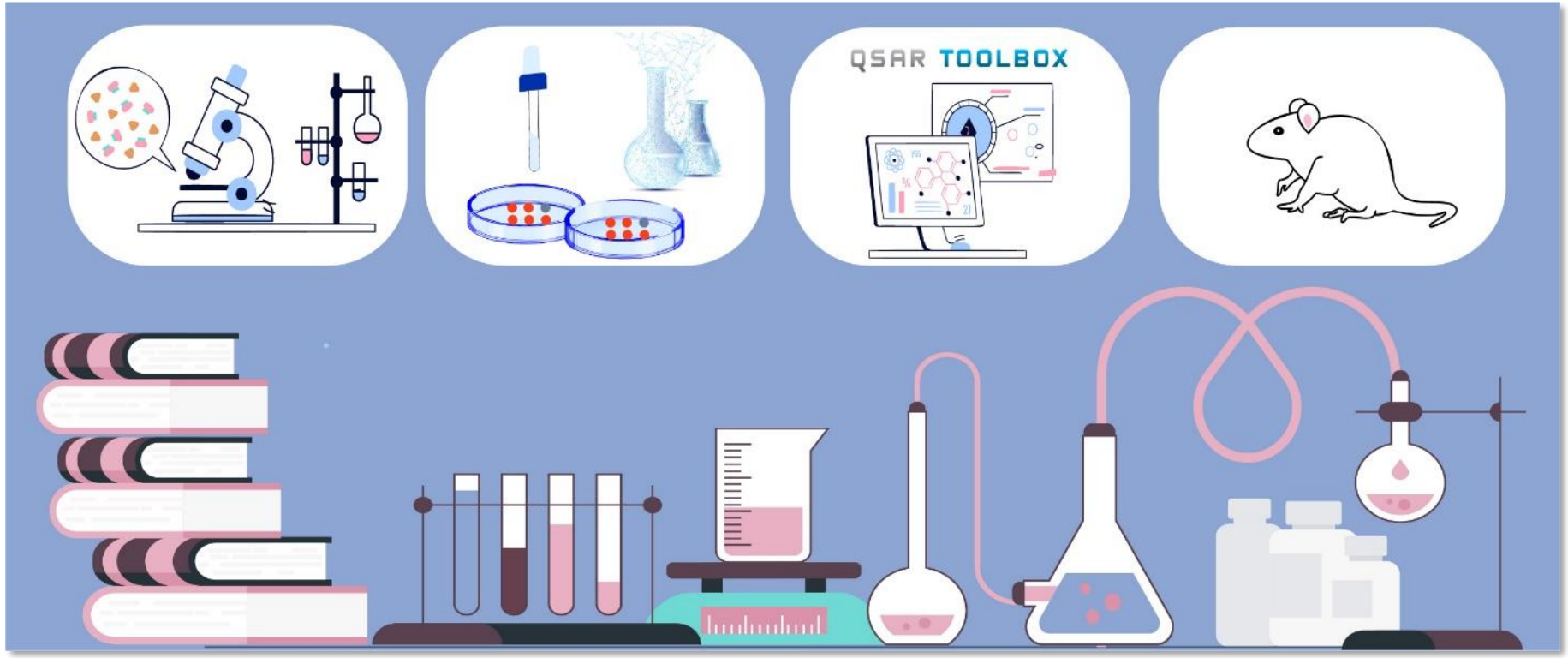
## GENERAL RECOMMENDATIONS

1. Principle of 3Rs (Replacement, Reduction and Refinement) : Pursuant to Chapter IV, section 17(2)(d) of the Prevention of Cruelty to Animals Act, 1960, which provides that "experiments on animals are avoided wherever it is possible to do so," the principles of 3Rs of animal use shall be taken into account in the fulfillment of registration requirements, taking particular account of the timely use of new validated 3Rs methods recognized by OECD and other regulatory authorities (with robust regulatory framework). Tests on vertebrate animals shall be undertaken judiciously. Alternative approaches to be considered shall include *in vitro* tests and non-testing approaches such as waivers, read-across (data bridging) and valid *in silico* models subject to **satisfaction** of the Registration Committee.
2. Acute Dermal & Skin Irritation studies may be combined
3. OECD 436 will be also accepted besides OECD 403 for Acute Inhalation

- **Implementation of 3Rs principle (replace, reduce and refine the use of animals in experimentation)**
- **Consider the use of all valid alternative approaches (*in vitro* methods and non-testing approaches—waivers, read-across and *in silico* models)**

**2017 Guidance Document on Toxicology for Registration of Chemical Pesticides**

# Tools to support an integrated testing approach




https://www.oecd.org/chemicalsafety/risk-assessment/iata/

- **All valid alternatives should be considered in an integrated testing approach. Animal testing should be considered only as a last resort**

# Skin and eye testing

## Eye irritation/corrosion

OECD TG 492: Reconstructed Human Cornea-like Epithelium (RhCE) Test Method for Identifying Chemicals Not Requiring Classification and Labelling for Eye Irritation or Serious Eye Damage (e.g. EpiOcular™, SkinEthic™, LabCyte, MCTT HCE™)

OECD TG 494: Vitrigel-Eye Irritancy Test (EIT) Method for Identifying Chemicals Not Requiring Classification and Labelling for Eye Irritation or Serious Eye Damage

OECD TG 496: In Vitro Macromolecular Test Method for Identifying Chemicals Inducing Serious Eye Damage and Chemicals Not Requiring Classification for Eye Irritation or Serious Eye Damage

OECD TG 467: Defined Approaches for Serious Eye Damage and Eye Irritation

OECD TG 460: Fluorescein Leakage (FL) Test Method for Identifying Ocular Corrosives and Severe Irritants

OECD TG 491: Short Time Exposure (STE) in vitro method

OECD TG 437: Bovine Corneal Opacity and Permeability (BCOP) Test Method for Identifying i) Chemicals Inducing Serious Eye Damage and ii) Chemicals Not Requiring Classification for Eye Irritation or Serious Eye Damage

OECD TG 438: Isolated Chicken Eye (ICE) Test Method for Identifying i) Chemicals Inducing Serious Eye Damage and ii) Chemicals Not Requiring Classification for Eye Irritation or Serious Eye Damage

## Skin irritation/corrosion

OECD TG 431: In Vitro Skin Corrosion: Reconstructed Human Epidermis Test Method

OECD TG 435: In Vitro Membrane Barrier Test Method for Skin Corrosion

OECD TG 439: In Vitro Skin Irritation: Reconstructed Human Epidermis Test Method

## Skin sensitisation

OECD TG 497: Defined Approaches on Skin Sensitisation

OECD TG 442c: In Chemico Skin Sensitisation-Assays Addressing the Adverse Outcome Pathway Key Event on Covalent Binding to Proteins

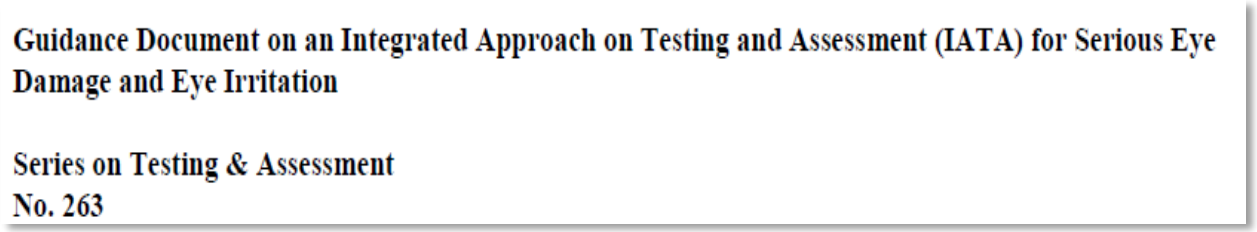
OECD TG 442d: In Vitro Skin Sensitisation-Assays Addressing the AOP Event on Keratinocyte Activation

OECD TG 442e: In Vitro Skin Sensitisation-Assays Addressing the Key Event Activation of Dendritic Cells

- **All internationally valid non-animal methods (*in chemicolin vitro* and *ex vivo*) are accepted in lieu of animal study, when scientifically justified**
- **A negative or a positive result in an *in chemicolin vitro* and *ex vivo* study will not trigger additional *in vivo* studies, when scientifically justified**

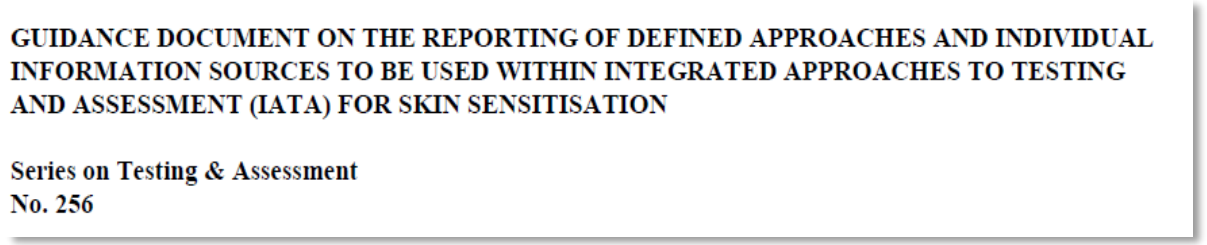
https://www.oecd-ilibrary.org/environment/oecd-guidelines-for-the-testing-of-chemicals-section-4-health-effects_20745788?page=1

# Use of integrated approach on testing and assessment- skin and eye testing



Guidance Document on an Integrated Approach on Testing and Assessment (IATA) for Serious Eye Damage and Eye Irritation

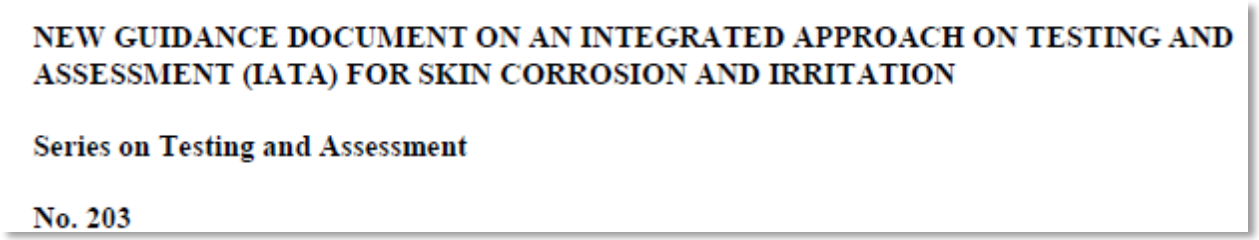
Series on Testing & Assessment
No. 263

https://www.oecd.org/officialdocuments/publicdisplaydocumentpdf/?cote=ENV-JM-MONO(2017)15/REV1%20&doclanguage=en


GUIDANCE DOCUMENT ON THE REPORTING OF DEFINED APPROACHES AND INDIVIDUAL INFORMATION SOURCES TO BE USED WITHIN INTEGRATED APPROACHES TO TESTING AND ASSESSMENT (IATA) FOR SKIN SENSITISATION

Series on Testing & Assessment
No. 256

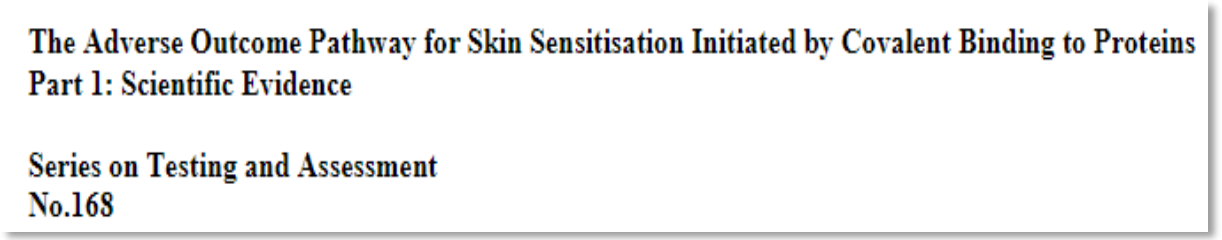
https://www.oecd.org/officialdocuments/publicdisplaydocumentpdf/?cote=env/jm/mono(2016)29&doclanguage=en


NEW GUIDANCE DOCUMENT ON AN INTEGRATED APPROACH ON TESTING AND ASSESSMENT (IATA) FOR SKIN CORROSION AND IRRITATION

Series on Testing and Assessment

No. 203

https://www.oecd.org/officialdocuments/publicdisplaydocumentpdf/?cote=ENV/JM/MONO(2014)19&doclanguage=en


The Adverse Outcome Pathway for Skin Sensitisation Initiated by Covalent Binding to Proteins Part 1: Scientific Evidence

Series on Testing and Assessment
No.168

https://www.oecd.org/officialdocuments/publicdisplaydocumentpdf/?cote=env/jm/mono(2012)10/part1&doclanguage=en

- **Integrated Approach on Testing and Assessment (IATA) should be applied for the assessment of eye/skin irritation-corrosion and skin sensitisation**

# Weight-of-evidence (WoE) approach

**Waiver would be considered only when existing information provides robust and full scientifically sound weight of evidence approach and read across/bridging from structurally and /or biologically related similar pesticides specifically case to case basis on full merits.**

**Examination of all *existing* data**

Epidemiological/clinical data

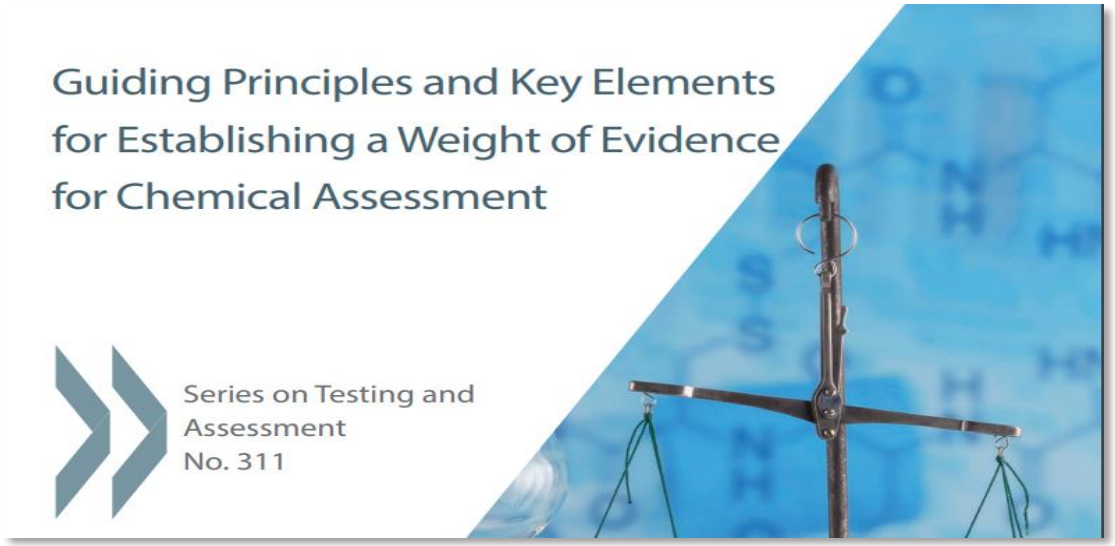
Experimental data
(animal/*in vitro/ex vivo/in chemico*)

**Non-testing strategies (read across/bridging from structurally/biologically related substances and QSARs)**

**Where data is insufficient?**

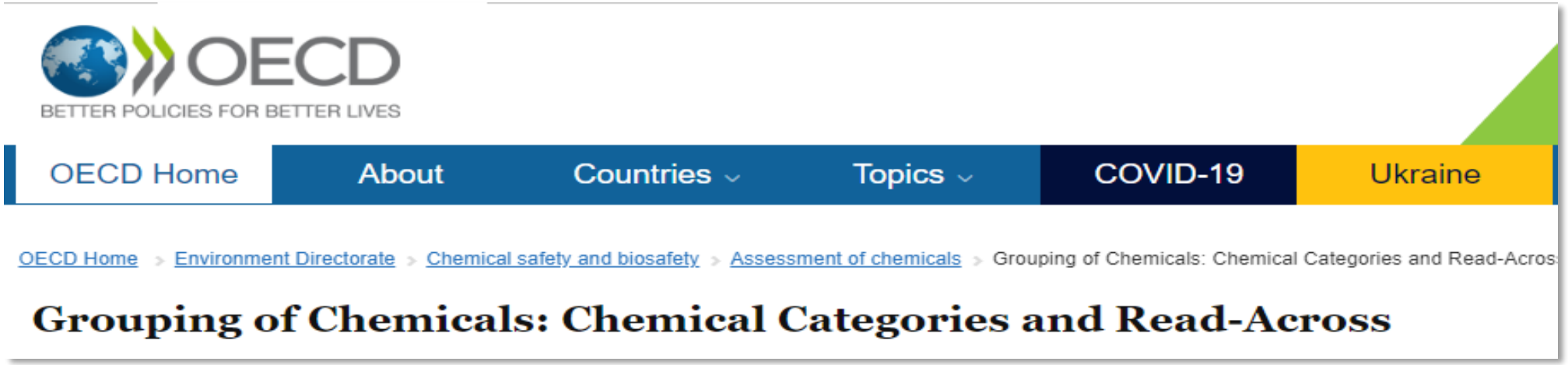
Conduct testing using non-animal methods

**Animal testing as last resort**




- **Registrants are encouraged to use a WoE approach considering all existing information**
- **If additional data needs to be generated, non-animal testing approaches should be used**

# Read-across



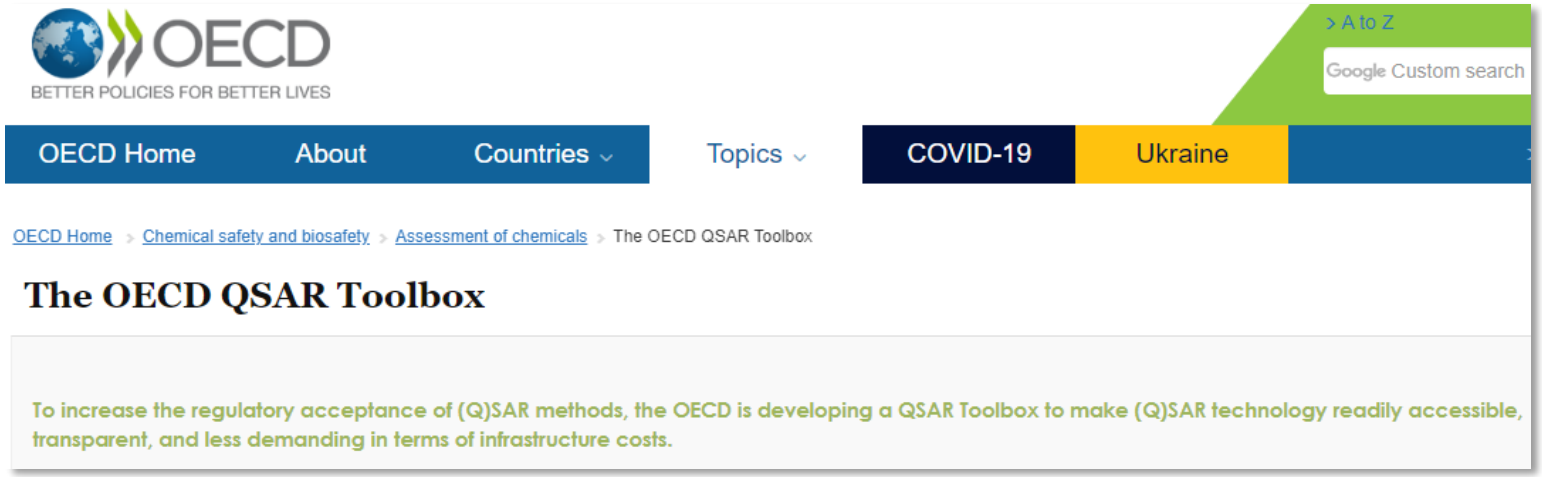

- Guidance on Grouping of Chemicals, second edition Series on Testing and Assessment No. 194, 2014

- Guidance Document for using the OECD (Q)SAR Application Toolbox to develop Chemical Categories according to the OECD Guidance on Grouping of Chemicals, Series on Testing and Assessment No.102, 2009

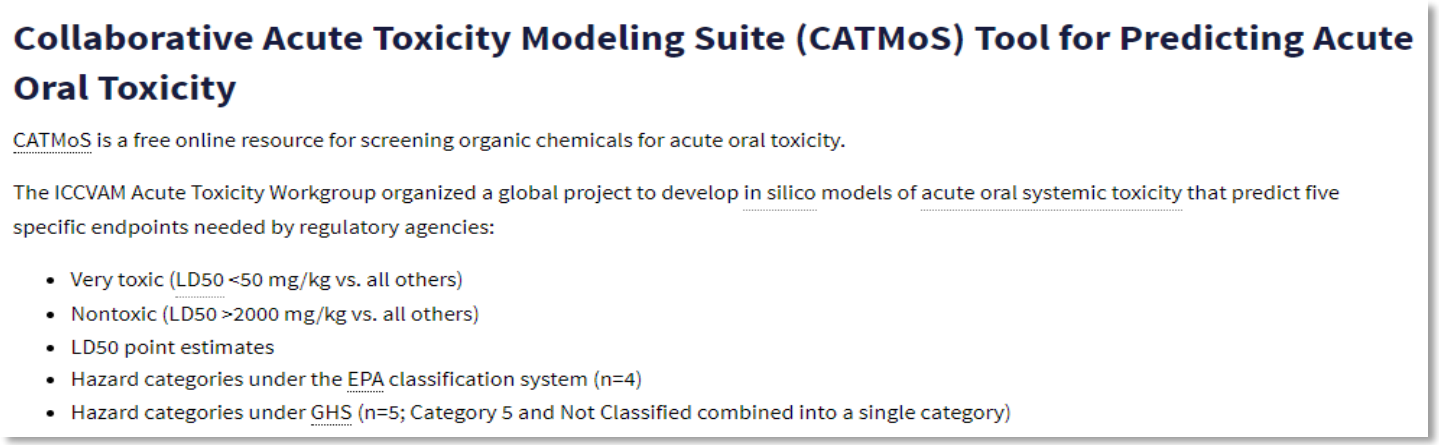
https://www.oecd.org/chemicalsafety/risk-assessment/groupingofchemicalschemicalcategoriesandread-across.htm

- **Registrants are encouraged to implement read-across/data bridging principles for chemically or biologically related pesticides**

# QSAR toolbox



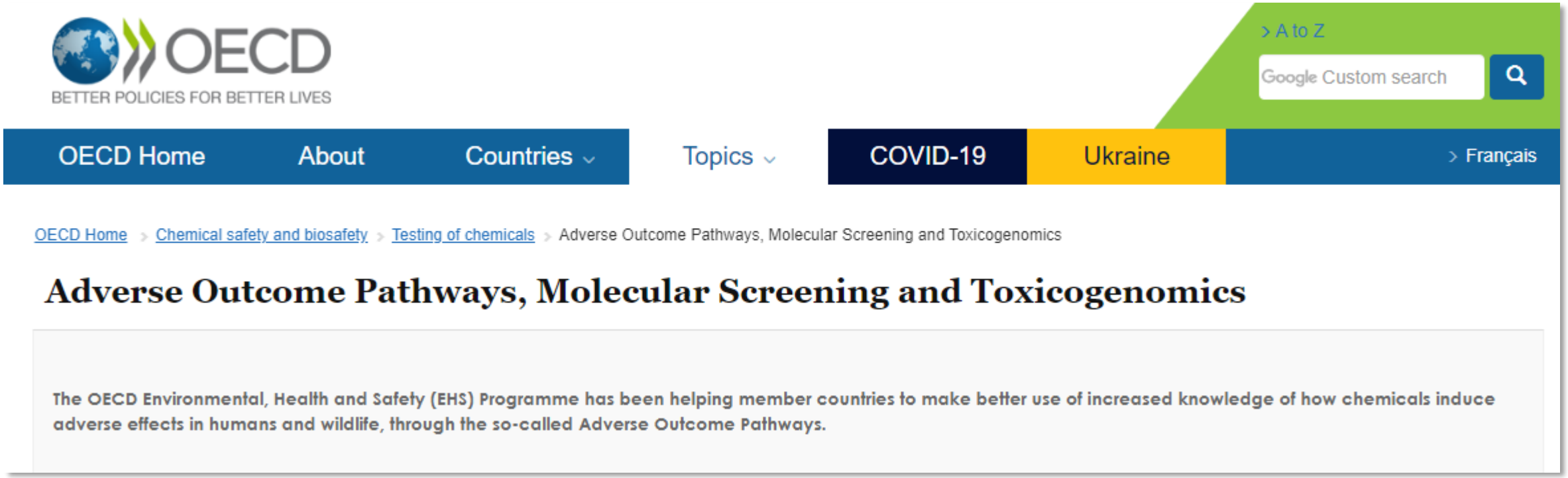

https://www.oecd.org/chemicalsafety/risk-assessment/oecd-qsar-toolbox.htm




https://ntp.niehs.nih.gov/iccvamreport/2019/technology/comp-tools-dev/catmos/index.html

➢ **Registrants are encouraged to implement valid QSAR approaches**

# Adverse outcome pathways (AOPs)




https://www.oecd.org/chemicalsafety/testing/adverse-outcome-pathways-molecular-screening-and-toxicogenomics.htm

- **Registrants are encouraged to use AOPs in an IATA framework**

# Waiver opportunities

**CIB&RC may accept waiver requests based on the following WoE approach (not exclusive):**

## Physicochemical/biological properties

- Acute oral study or eye/skin irritation/corrosion study *may not* be required if:
  - ✓ the substance or formulation is a strong acid (pH ≤ 2.0) or base (pH ≥ 11.5) and the available information indicates that it should be classified as corrosive or severely irritating
- Acute inhalation may not be required if:
  - ✓ the vapour pressure is low i.e. <10-2 Pa under practical conditions

## Technical feasibility

- Acute oral study *may not* be required if:
  - ✓ the test substance is a gas or vapour at ambient temperature
- Acute inhalation study may not be required if:
  - ✓ the test substance is not a gas or liquefied gas

## Use and exposure patterns

- Acute dermal study or skin irritation/corrosion study *may not* be required if:
  - ✓ skin contact is unlikely in production or use or the product design prevents dermal exposure
- Acute inhalation study may not be required if:
  - ✓ The test substance is not included in products that are powders or are applied by spraying

# Examples of waiver opportunities

**I. Acute Mammalian Toxicity Studies**

| S.No. | Toxicity Study | Technical | Formulation |
|---|---|---|---|
| 01. | Acute Oral - Rat | R | R |
| 02. | Acute Dermal – Rat / Rabbit | R | R |
| 03. | Acute Inhalation | $R^1$ | $R^1$ |
| 04. | Primary Skin Irritation | $R^2$ | $R^2$ |
| 05. | Acute Eye Irritation | $R^3$ | $R^3$ |
| 06. | Skin Sensitization* | R | R |

**$R^1$**: Not required when :

a) Vapour pressure is low i.e. $<1x10^{-2}$ Pa under practical temperature conditions of India (up to $20^0$C). or

b) Technical Grade Active Ingredient (TGAI) does not contain particles of diameter of < 30µm (> 1% on w/w basis)

**$R^2$**: The assessment of this endpoint shall be carried out according to a sequential testing strategy as follows:

(1) the assessment of dermal corrosivity using a validated in vitro test method;

(2) the assessment of dermal irritation using a validated in vitro test method;

(3) An In vivo dermal irritation study.

*In vivo* testing should not be conducted if:

a) The substance or formulation is a strong acid (pH ≤ 2,0) or base (pH ≥ 11,5) and the available information indicates that it should be classified as skin corrosive. or

b) the substance is classified as acutely toxic by the dermal route

**$R^3$**: Testing need not be performed if the available information indicates that the substance should be classified as corrosive or severely irritating to the skin, e.g., if the substance is a strong acid (pH < 2.0) or base (pH > 11.5).

***In-vitro* study on case to case basis may be accepted.**

**II. Short Term Repeated Dose Toxicity Studies**

| S.No. | Toxicity Study | Technical | Formulation |
|---|---|---|---|
| 01. | Repeated Dose Range Finding Oral Toxicity Study (upto 28 Days) | $R^1$ | NR |
| 02. | Repeated Dose 90 Day Oral :<br>a) Toxicity Study-Rodent<br>b) Toxicity Study-Non Rodent (Dog)* | R | NR |
| 03. | Repeated Dose Dermal Toxicity | R | NR |
| 04. | Repeated Dose Inhalation Toxicity | $R^2$ | NR |

**$R^1$ :** This study is generally done to establish dose range but may not necessarily be conducted for a duration of 28 days.

**$R^2$** Not required when :

a) Vapour pressure is low i.e. <1x10-2 Pa under practical temperature conditions of India (up to 20oC). or

b) Technical Grade Active Ingredient (TGAI) does not contain particles of diameter of < 30µm (> 1% on w/w basis)

*Published literature from reliable source maybe acceptable.

**2017 Guidance Document on Toxicology for Registration of Chemical Pesticides**

- **Registrants are encouraged to consult with CIB&RC toxicology expert on their data needs and waiver opportunities before they begin testing**

# Waiver opportunities—references

**Replace** testing on animals

- Guidance document on considerations for waiving or bridging of mammalian acute toxicity tests
- Short guidance on threshold approach for acute fish toxicity

- Skin Sensitization Policy
- Mixtures Equations Pilot
- Alternative Testing Framework for Classification of Eye Irritation Potential of EPA-Regulated Pesticide Products
- New Approach Methodology (NAM) for Inhalation Risk Assessments
- Collaborative Acute Toxicity Modelling Suite (CATMoS)
- CompTox Chemicals Dashboard
- ECOTOX Knowledgebase

**Reduce** testing on animals

- Acute Toxicity Waiving and Bridging Guidance
- Acute Dermal Toxicity Tests for Pesticide Single-Active Ingredient
- Acute Dermal Toxicity Waiver Guidance for Pesticide Formulations
- Neurotoxicity Battery, Subchronic Inhalation, Subchronic Dermal and Immunotoxicity Studies
- Part 158 Toxicology Data Requirements & Hazard and Science Policy Council (HASPOC)
- Sub-Acute Avian Dietary Test Waiver Guidance
- Chemistry and Acute Toxicology Science Advisory Council (CATSAC)
- M010 – Substantially similar determination

https://www.epa.gov/pesticide-science-and-assessing-pesticide-risks/strategic-vision-adopting-new-approach-1

# Waiver opportunities—references

Health Canada

Guidance for Waiving or Bridging of Mammalian Acute Toxicity Tests for Pesticides
Acute Dermal Toxicity Waiver

Australian Government
Australian Pesticides and Veterinary Medicines Authority

In certain cases, you may provide scientific argument based on accepted scientific principles or data published in peer-reviewed journals in lieu of submission of toxicology studies

EURL ECVAM
European Union Reference Laboratory for Alternatives to Animal Testing

Strategy to Avoid and Reduce Animal Use in Genotoxicity Testing
Strategy to Replace, Reduce and Refine the use of Fish in Aquatic Toxicity and Bioaccumulation Testing

# Acceptance of non-animal approaches

**The replacement alternatives not involving experiments on animals would not be normally considered,except in exceptional and rare cases where in case of alternatives if available with full and sound justification is provided specifically case to case basis on merit subject to full satisfaction of the expert regarding full toxicity data provided for the alternatives.**

- **'Replacement alternatives': *in silico*, *in chemico*, *in vitro*, *ex vivo* approaches, read-across/data bridging, and waivers based on a WoE approach**
- **All 'replacement alternatives' not involving experiments on animals would be considered for registration when scientifically robust toxicity data is provided**

# Toxicity data requirements

Minutes of 442nd RC meeting held on 18.11.2022

C. **TOXICITY**

| Sl. No. | Parameters | Technical | | Formulation | | Technical/ Formulation | |
|---|---|---|---|---|---|---|---|
| | | 9(3b) | 9(3) | 9(3b) | 9(3) | 9(4) | 9(4) |
| | | TI/TIM | TI/TIM | FIM | FIM/FI | TIM | TI/FIM/FI |
| 1. | Acute oral Rat | R | R | R | R | NR | NR |
| 2. | Acute Dermal- Rat/ Rabbit | R | R | R | R | NR | NR |
| 3. | Acute inhalation-Rat | R | R | R | R | NR | NR |
| 4. | Primary Skin Irritation-Rabbit | R | R | R | R | NR | NR |
| 5. | Acute Eye Irritation-Rabbit | R | R | R | R | NR | NR |
| 6. | Skin Sensitization Test–Guinea Pig | R | R | R | R | NR | NR |

**2022 Guidelines/Data requirement for grant of registration under various categories: Chemical pesticides**

R: Required
NR: Not required

# Toxicity data requirements—chemical pesticides

- **Repeated dose 90 days oral toxicity study (Dog):** Peer reviewed international published literature is also acceptable

- **Carcinogenicity & chronic toxicity study** should be **combined** when testing is required

- **Ecotoxicity:** **Only single species required** for repeated dose and reproduction avian study, and acute toxicity in fresh water fish

- **TI from new source u/s 9(3):** Toxicity data **required only** for acute and repeated dose studies, mutagenicity, medical data, human toxicity data from other countries and International report on Carcinogenicity & Genotoxicity

- **TIM u/s 9(3):** In case same technical is registered for import or formulation made from the same technical is registered for import or indigenous manufacture, **acute toxicity and mutagenicity studies are only required** (if the identified impurities are within limits or beyond limits but not toxic)

- **TIM u/s 9(3):** In case same technical is registered for import or formulation made from the same technical is registered for import **BY THE SAME APPLICANT WITH SAME COMPOSITION, PROCESS OF MANUFACTURE ETC., data on Ames Test only is only required**.

**TI:** Technical import
**TIM:** Technical indigenous manufacture

# Toxicity data requirements—chemical pesticides

- **9(4) 'me too' registrants:** **No toxicity data would be required** for technical (TI/TIM) and formulation (FI/FIM) if the chemical equivalence is already established with the 9(3) registrants

- **Long lasting impregnating nests (LLIN):** **Acute toxicity studies only are required** with Premix along with health monitoring studies in users

- **Manufacturing Use Product (MUP):** **Acute toxicity studies only are required.** If the technical grade pesticide from which MUP is to be prepared is not registered, complete data would be required

- **Household pesticide formulations:** **Acute toxicity studies only are required** (for pesticides in solid & liquid form) along with data on technical. In case of pesticides in vapour form**,** health monitoring study of the user is required

- **Pesticide Formulation for use in Public Health:** **Acute toxicity studies, acute and repeated dose avian studies and acute fresh water fish are only required**

- **Formulation for use for Aircraft Disinfection:** If the technical grade is already registered, **acute toxicity data is only required**

**TI:** Technical import
**TIM:** Technical indigenous manufacture
**FI:** Formulation import
**FIM:** Formulation indigenous manufacture

# Toxicity data requirements—microbial pesticides

- **Inhalation toxicity study**: **Required only** for registration of entomopathogenic/entomotoxic bacteria
- **Pulmonary toxicity study: Required only** for registration of antagonistic bacteria, antagonistic fungi, entomopathogenic fungi and baculovirus
- **Intraperitoneal toxicity study: Required only** for registration of antagonistic fungi, entomopathogenic fungi and antagonistic bacteria
- **Cell culture and Intravenous study**: **Required only** for registration of baculovirus
- **Toxicity to honey bees: Required only** for registration of entomopathogenic/entomotoxic bacteria and antagonistic fungi
- **Toxicity to silkworm: Required only** for registration of antagonistic fungi
- **Avian and fresh water toxicity study: Only one species requirement**

# Toxicity data requirements—microbial pesticides

- **No toxicity data required** for previously registered strain from the same source with same strain designation and accession number
- If genome sequence of conserved region of the microbial strains/microbes used as microbial pest control agent is identical with previously registered strain, **no toxicity data is required**
- If formulations are developed from similar previously registered mother culture using similar ingredient and process of manufacture then **no toxicity data is required**

# Toxicity data requirements—botanical pesticides

- **9(4) 'me too' registrants:** **No toxicity data** would be required for technical and formulation if the chemical equivalence is already established with the 9(3) registrants

    - **Extract u/s 9(4):** It shall be obtained from the same part of the plant with same process of extraction and should have identical chemical composition as of 9(3) registrant.
    - **Formulation u/s 9(4):** It should have identical chemical composition and required to be prepared from the extract already registered for use in the country.

- **Sub-acute studies (extract):** There is **no default requirement of sub-acute toxicity studies for extract** and shall be determined on the basis of acute toxicity study report. **Registrants are encouraged to consult with the CIB&RC toxicity expert before they begin higher testing**

- **Sub-acute studies (formulation):** **No requirement of sub-acute and long term toxicity studies for formulations**

# Toxicity data requirements—semiochemicals/pheromones

- **9(4) ‘me too’ registrants:** **No toxicity data** would be required for technical if the chemical equivalence is already established with the 9(3) registrants

- **9(3b) registrants:** **No sub-acute toxicity data required,** except teratogenicity

- **Formulation products:** **No toxicity data required** unless it is added with some other pesticides

- **Lepidopterean pheromones** that are naturally occurring compound designated by an unbranched aliphatic chain (between 9 and 18 carbons) ending in an alcohol, aldehyde or acetate functional group and containing up to 3 double bonds in aliphatic backbones **can be exempted from the sub-acute toxicity, carcinogenicity, effect on reproduction and metabolism** if their use rates do not exceed 150 gm/acre/year with Good Agricultural Practices and used in solid matrix dispensers.

# Additional considerations for pesticide registration

- All published literature (peer-reviewed) and data submitted for registration of pesticides in other countries maybe be considered for registration in India, including for pesticides being registered for the first time in the country

- In case of a change in the manufacturing site (in India and globally), **no new toxicity data** needs to be generated if the registrant can establish that there is no change in the chemical equivalence of the pesticide

# General benefits of using new approach methodologies

- More fit for purpose and reliable offering better protection of human health and environment
- Less resource intensive and faster (expedite pesticide registration process)
- Avoid duplication of toxicity data generation
- Facilitate international harmonisation
- Reduction in animal suffering

# Key-take away points

- Ensure implementation of 3Rs principle (replace, reduce and refine the use of animals in experimentation)
- Consider the use of all valid alternative approaches (*in silico*, *in chemico*, *in vitro*, *ex vivo* testing approaches and non-testing approaches—waivers, read-across and *in silico* models) in an integrated testing approach
- All internationally valid non-animal methods (*in chemico*/*in vitro* and *ex vivo*) are accepted in lieu of animal study, when scientifically justified. A negative or a positive result in an *in chemico*/*in vitro* and *ex vivo* study will not trigger additional *in vivo* studies, when scientifically justified
- Integrated Approach on Testing and Assessment (IATA) should be applied for the assessment of eye/skin irritation-corrosion and skin sensitisation
- Waivers will be accepted on a WoE approach when scientifically sound justification is provided
- Registrants are encouraged to discuss specific data requirements and waiver opportunities before they begin toxicity testing

# Thank you