

# toxicology and regulatory news

December 2023



## The UK REACH transition

In response to concerns raised by the chemical industry about the significant cost of accessing EU data packages to support UK REACH transitional registrations, DEFRA has worked alongside the Health and Safety Executive (HSE) and Environment Agency (EA) to propose the Alternative Transitional Registration model (ATRm). This is a new approach to UK REACH which aims to reduce the cost of registration while ensuring high levels of human health and environmental protection. It appears that there will be a greater emphasis on use and exposure information, whilst the hazard information required for transitional registrations and intermediates will be reduced to an “essential minimum”. With hazard information available on over 22,000 chemicals commonly used in Europe, it was noted that “our regulators do not need to hold a complete replica of all the registration data on all chemical substances held under EU REACH”. A more targeted approach was described, in which available information on emerging areas of risk would be focused on to shape regulatory priorities.

More details on these proposed policy changes are expected in early 2024.

Department for Environment, Food and Rural Affairs (2023). [UK REACH Alternative Transitional Registration model \(ATRm\)](#).

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- Pertinent pronouncements on **toxicology** from national and international authorities, government departments and other expert groups
- Major health-related findings (including key legislative developments) that may affect **product safety** and **regulatory acceptability**

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## International

### OECD...

#### ...updates Test Guideline (TG) 467 on eye irritation

OECD has drafted an update to TG 467 on Defined Approaches (DAs) for serious eye damage and eye irritation to incorporate Part 3 of the guideline, which describes a DA based on *in vitro* data requirements for neat solids. It encompasses the Bovine Corneal Opacity and Permeability (BCOP) test using the laser light-based opacitometer (TG 437) and the SkinEthic™ human corneal epithelium eye irritation test (TG 492) and can be used for discriminating between the three United Nations Globally Harmonized System of Classification and Labelling of Chemicals (UN GHS) categories (1, 2 and no Category). The performance of the DA was evaluated using 109 solid test materials with curated *in vivo* (Draize) eye test reference data and demonstrated a balanced accuracy (average between sensitivity and specificity) of 66.7%.

Organisation for Economic Cooperation and Development (2023). [Draft Updated TG 467 Part III: Defined approach on eye irritation for solids.](#)

#### ...draft guidance document for assessing serious eye damage and eye irritation

In recent years, a number of test guidelines on *in vitro* methods have been adopted and/or revised for identifying test chemicals that either induce serious eye damage or do not require classification for eye irritation and serious eye damage. There are also methods not adopted by the OECD that may provide information that is required by some authorities. The OECD has therefore updated its guidance document to establish Integrated Approaches to Testing and Assessment (IATA) for serious eye damage and eye irritation hazard identification. It describes the various types of information sources comprising the IATA (e.g., physico-chemical properties, *in vitro* and *in chemico* test methods) and their key characteristics, providing guidance on which information sources or assay types would be most conducive to a conclusion on classification.

Organisation for Economic Cooperation and Development (2023). [Guidance document No 263 on Integrated Approaches to Testing and Assessment \(IATA\) for serious eye damage and eye irritation \(second edition\).](#) ENV/JM/MONO(2017)15/REV1.

## ...develops Performance Standards on the Epidermal Sensitisation Assay (EpiSensA)

An OECD “Performance Standards” document has been drafted on the validation of new or modified EpiSensA *in vitro* methods, designed to provide information on Key Event 2 in the Adverse Outcome Pathway (AOP) for skin sensitisation by measuring certain genetic markers associated with the keratinocyte response. Guidance is provided on evaluating the reliability and relevance of these test methods which, if successfully validated, may be added to OECD Test Guideline 442D.

Organisation for Economic Cooperation and Development (2023). [Draft performance standards for assessment of proposed similar or modified in vitro skin sensitisation epidermal sensitisation assay \(EpiSensA\) test methods \(Intended for the developers of new or modified similar test methods\)](#).

## FAO and WHO...

### ...fish consumption and health risks

The summary and conclusions of the Joint FAO/WHO Expert Consultation on the risks and benefits of fish consumption, held in October 2023, have been released. The Joint Committee evaluated the data issued since it first considered this topic in 2010, to determine the health effects of exposures to dioxins, dioxin-like polychlorinated biphenyls (dl-PCBs) and methylmercury present in fish. Although evidence suggests that dioxins and dl-PCBs are associated with reduced semen quality, altered sex ratio and weaker tooth enamel in humans, the Expert Consultation could not draw a firm conclusion regarding the association with fish consumption. There is also limited evidence of adverse health effects from exposures to methylmercury as a result of fish consumption. Further research is needed to estimate the association of fish intake with adverse health effects and to better elucidate the contribution of dioxins, dl-PCBs and other contaminants from fish consumption to human health outcomes.

Food and Agriculture Organisation of the United Nations and World Health Organization (2023). [Summary and conclusions. Issued in November 2023. Joint FAO/WHO Expert Consultation on Risks and Benefits of Fish Consumption. FAO, HQ, Rome, Italy: 9 – 13 October 2023.](#)



## ...Reference Dose (RfD) values for certain food allergens

The FAO and WHO have released Part 5 of its series on risk assessment of food allergens, evaluating the allergenicity of certain tree nuts, soy, celery, lupin, mustard, buckwheat and oats. Oral RfDs of 1 mg/day have been proposed for celery, mustard and tree nuts (Brazil, macadamia and pine), and 10 mg/day for buckwheat, lupin and soy. No RfD could be established for oats.

Food and Agriculture Organisation of the United Nations and World Health Organization (2023). [Risk Assessment of Food Allergens – Part 5: Review and establish threshold levels for specific tree nuts \(Brazil nut, macadamia nut or Queensland nut, pine nut\), soy, celery, lupin, mustard, buckwheat and oats](#). Food Safety and Quality Series, No. 23. Rome.

## Europe

### ECHA...

#### ...adds new pharmaceutical data to IUCLID

Toxicity data provided by the FDA for 180 approved pharmaceuticals have been released in IUCLID format, adding to the already published 348 datasets. The data include results from reviews of repeated-dose toxicity, carcinogenicity, and developmental/reproductive toxicity studies, as well as clinical human data. The information should help in the development of predictive models and can be used to analyse correlations between non-human and human data.

European Chemicals Agency (2023). [ECHA adds new pharmaceutical data to IUCLID](#).

#### ...releases statement on REACH-IT

In April 2024 (delayed from the original plan of January 2024), ECHA will be withdrawing the dossier preparation function in REACH-IT for Downstream user notifications of authorised uses and Classification and Labelling (C&L) notifications. So, from then, all submissions in REACH-IT must be made by uploading a IUCLID dossier.

European Chemicals Agency (2023). [More time for online dossiers](#).

### **...derives Occupational Exposure Levels (OELs) for boron (and borates)**

An 8-hour Time-Weighted-Average (TWA) limit value of 1.3 mg B/m<sup>3</sup> was established, with the critical effect being developmental toxicity at the Lowest-Observed-Adverse-Effect Level (LOAEL) of 13.3 mg B/kg bw/day in an oral study on boric acid given to pregnant rats.

A Short-Term (15-minute) Exposure Limit (STEL) of 0.75 mg B/m<sup>3</sup> was identified, based on nasal secretion and eye irritation seen at 1.5 mg B/m<sup>3</sup> in a study on healthy volunteers exposed to airborne sodium tetraborate pentahydrate.

European Chemicals Agency (2023). [ECHA scientific report for evaluation of limit values for boron and its compounds at the workplace.](#)

### **...RAC and SEAC opinions on MCCP and related substances**

In September 2022, ECHA proposed restricting the use of medium-chain chlorinated paraffins (MCCP) and other substances that contain chloroalkanes with carbon chain lengths within the range of C14 to C17. ECHA's Committees for Risk Assessment (RAC) and Socio-Economic Analysis (SEAC) have now released their opinions, adopting the proposed restriction that limits the presence of the C14 to C17 chloroalkanes in substances, mixtures and articles to less than 0.1% w/w.

European Chemicals Agency (2023). [Opinion on an Annex XV dossier proposing restrictions on Medium-chain chlorinated paraffins \(MCCP\) and other substances that contain chloroalkanes with carbon chain lengths within the range from C14 to C17.](#)

### **...authorisation applications for four REACH substances**

ECHA has issued a call for comments (by 10<sup>th</sup> January 2024) on applications for the authorisation of specific uses of the following substances:

- 4-nonylphenol, branched and linear, ethoxylated (various uses)
- potassium dichromate (single use)
- bis(2-ethylhexyl) phthalate (various uses)
- tetraethyllead (single use)
- 4-(1,1,3,3-tetramethylbutyl)phenol, ethoxylated (various uses)

European Chemicals Agency (2023). [Applications for authorisation – current consultations.](#)

### **...calls for evidence on octocrilene**

The information collected through this call for evidence, which has a deadline of 10<sup>th</sup> January 2024, will be used to prepare an Annex XV restriction dossier on octocrilene (used in consumer products for its UV filter/absorber and stabilisation properties), to document the feasibility of alternatives, and to report on the socio-economic impacts of a use restriction.

European Chemicals Agency (2023). [Current calls for comments and evidence](#).

### **...requests data on *in vivo* testing proposals for REACH substances**

ECHA has requested information from third parties by 18<sup>th</sup> December on testing proposals for various REACH substances, notably 1,2,3,6-tetrahydromethyl-3,6-methanophthalic anhydride (for reproductive toxicity) and lithium chloride (for genotoxicity).

European Chemicals Agency (2023). [Testing proposals for submission by 18<sup>th</sup> December 2023](#).

### **...proposals for Harmonised Classification and Labelling (CLH)**

Under the EU Classification, Labelling and Packaging (CLP) regulation, there is a legal obligation for suppliers to evaluate the hazards of chemicals (substances and mixtures) that are to be placed on the market, and to classify and label them appropriately. An option also exists for Member State Competent Authorities or industry to propose CLH of a substance across Europe. Following the submission of a CLH proposal, ECHA organises a public consultation period of 60 days. Under this scheme, CLH reports have been submitted by authorities in Belgium, Denmark, the Netherlands, and Norway to standardise the classification and labelling of the following substances:

- 2-pyrrolidone (for reproductive toxicity)
- cinmethylin (for several human health and physical hazards)
- ethylene bis[3,3-bis(3-tert-butyl-4-hydroxyphenyl)butyrate] (for reproductive toxicity)
- metam-sodium and -potassium (for several human health and physical hazards)
- methyl isothiocyanate (for several human health and physical hazards)
- tebuconazole (for several human health hazards)

European Chemicals Agency (2023). [Harmonised classification and labelling consultations](#).

## Biocidal Products Regulation...

### ...consultation on substitution of three REACH substances

ECHA has launched a call for information on the availability of substitutes or alternatives to the following biocidal active substances: dinotefuran and prallethrin for Product-Type (PT) 18 (insecticides, acaricides and products to control other arthropods), medetomidine for PT 21 (antifouling products) and polymeric betaine for PT 8 (wood preservatives).

European Chemicals Agency (2023). [Public consultation on potential candidates for substitution. Deadline 4<sup>th</sup>/22<sup>nd</sup> January 2024.](#)

### ...consultation on exclusion criteria derogation for DBNPA

Intended for use in the short-term preservation of mineral slurry prior to its use in paper mills (PT 6), 2,2-dibromo-2-cyanoacetamide (DBNPA) is subject to a public consultation on whether the conditions for derogation are met, as set out in Article 5(1) of the Biocidal Products Regulation.

European Chemicals Agency (2023). [Public consultation on derogation to the exclusion criteria. Deadline 4<sup>th</sup> January 2024.](#)

## EFSA...

### ...peer review of metalaxyl-M, dimoxystrobin and mecoprop-P

EFSA has carried out a peer review of the initial human health risk assessments of the pesticide active substances, metalaxyl-M and dimoxystrobin. The reports outline the reliable endpoints for use in regulatory risk assessment and identify outstanding areas of concern and data gaps.

In addition, EFSA has updated its conclusion on the peer review of the pesticide risk assessment of mecoprop-P with regards to its endocrine-disrupting properties, concluding that exposure is not expected to cause endocrine disruption in humans and non-target organisms.

European Food Safety Authority (2023).

[Peer review of the pesticide risk assessment of the active substance dimoxystrobin. EFSA Journal 21\(10\), 8329.](#)

[Peer review of the pesticide risk assessment of the active substance metalaxyl-M \(amendment of approval conditions\). EFSA Journal, 21\(10\), 8373.](#)

[Updated conclusion on the peer review of the pesticide risk assessment of the active substance mecoprop-P. EFSA Journal 21\(10\), 8344.](#)

## ...in other news...

EFSA's Pesticides Peer Review Unit has launched two open consultations on the active substance, paraffin oils, one relating to CAS RN 72623-86-0 and the other to CAS RN 97862-82-3. In addition, a consultation on clomazone in the context of endocrine disruption has also been released.

European Food Safety Authority (2023). [Pesticides Peer Review Unit](#).

The FEEDAP Panel has released opinions on the safety and efficacy of the following animal feed additives:

- 41 compounds providing a herbal flavour
- coriander oil
- dicopper chloride trihydroxide
- manganese(II)-betaine complex
- star anise terpenes

European Food Safety Authority (2023). [Panel on Additives and Products or Substances used in Animal Feed \(FEEDAP\)](#).

## EMA releases draft herbal monograph and assessment report on pelargonium root

EMA's Committee on Herbal Medicinal Products (HMPC) has released a draft EU herbal monograph on pelargonium (*Pelargonium sidoides* or *reniforme*) root, used to fight common colds and infections of the respiratory tract or ear. The monograph is released along with an assessment report that summarises the available toxicity data.

European Medicines Agency (2023). [Pelargonii radix. Draft EU herbal monograph, assessment report and references](#).

## BfR...

### ...report on the consumption of vitamin D supplements

Vitamin D plays a key role in the development and maintenance of a well-functioning immune system, and healthy bones and muscles. While daily supplementation of up to 20 µg is not associated with adverse health effects, high-dose supplements (providing 100 µg/day or more), in conjunction with other sources of exposure, have the potential to harm human health.

German Federal Institute for Risk Assessment (BfR) (2023). [\[Dietary supplements with vitamin D – useful or superfluous?\] \(in German\). BfR Opinion 055/2023](#).

### **...opinion on antiperspirants containing aluminium**

Aluminium salts, in particular aluminium chlorohydrate, are active ingredients in some antiperspirants, temporarily blocking sweat pores to prevent perspiration, and also exhibiting an antibacterial effect. BfR has evaluated the health risks associated with topical aluminium application. It was noted that new studies have shown it to have an extremely low bioavailability (about 0.002%) via this route. Having reviewed the available toxicological data, BfR concluded that the likelihood of impairments to health from daily use of antiperspirants is low, but that it is important to also consider total exposures to aluminium from all sources (including the diet).

German Federal Institute for Risk Assessment (BfR) (2023). [New studies on antiperspirants containing aluminium: impairments to health unlikely as a result of aluminium uptake via the skin. BfR Opinion 045/2023.](#)

### **...evaluation of oral hexahydrocannabinol (HHC)**

HHC is a cannabinoid present in gummies and dietary supplements that may be incorrectly perceived as foods. Available human and laboratory animal data suggests that HHC is psychoactive, with similar effects to THC, albeit with a lower potency. Although the available toxicity data on HHC are insufficient to accurately evaluate the health risks of excessive intake, for example by children, BfR noted that its accidental consumption could result in intoxication.

German Federal Institute for Risk Assessment (BfR) (2023). [Hexahydrocannabinol \(HHC\) in foodstuffs: evidence of psychoactive effects. BfR Opinion 044/2023.](#)

### **RIVM...**

#### **...updated review of the health effects of wood smoke**

An updated literature review of the health effects of wood smoke has a similar bottom line to previous RIVM evaluations on this complex mixture. Although wood smoke contains substances that are harmful to human health, no firm conclusions could be drawn on the health risks posed to people burning wood, or to other exposed individuals. Better and more extensive research is required, particularly in terms of accurately estimating indoor and outdoor exposure levels.

Dutch National Institute for Public Health and the Environment (RIVM) (2023). [\[Health consequences of wood smoke: an update of an exploratory literature review\] \(in Dutch\). RIVM letter report 2023-0335.](#)

## ...evaluation of chromium VI

RIVM has updated its review of the adverse health effects of chromium VI, which has been linked to adverse health conditions in workers, including nasal cavity ulceration, chronic lung disease, allergy, and various types of cancer (e.g., of the lung and nasal cavity; it is also suspected of causing laryngeal and stomach cancer). As part of this project, but published separately, RIVM analysed the human data on chromium VI and cancer of the oral cavity, small intestine, pancreas, prostate and bladder, finding “no clear link to occupational exposure”.

Dutch National Institute for Public Health and the Environment (RIVM) (2023).

[\[Adverse health effects and diseases caused by chromium-6. Third update of the scientific literature\] \(in Dutch\). RIVM letter report 2023-0365.](#)

[\[Meta-analysis of epidemiological studies on the relationship between occupational exposure to chromium-6 and cancer of the oral cavity, small intestine, pancreas, prostate and bladder\] \(in Dutch\). RIVM report 2023-0269.](#)

## NEG report on occupational chemical exposures and unusual working hours

This Nordic expert group has reviewed the available scientific data on the combined effects of chemical exposures and unusual working hours, in the context of Occupational Exposure Limits (OELs) that are typically designed for 8 hours of work during the day, and a 5-day working week. Human and laboratory animal studies suggest that the time of day (or night) that exposure occurs may affect chemical biotransformation and toxicity. Although the available data were not considered sufficient to make recommendations on how to adjust OELs for working at different times of the day/night, methods were proposed to adjust OELs for shorter or extended working hours.

The Nordic Expert Group for Criteria Documentation of Health Risks from Chemicals (NEG) (2023). [155. Occupational chemical exposures in combination with unusual working hours. Nr 2023; 57\(2\).](#)

## United Kingdom

### HSE...

#### ...risk assessment and proposed restriction of lead ammunition

The HSE, as the Agency for UK REACH, has prepared an Annex 15 restriction dossier in which the risks of lead to human health (via food consumption) and the environment (as a result of leaching) are assessed in the context of live quarry and outdoor target shooting with lead-containing ammunition. It found that there is a human health risk to consumers of high volumes of game meat (particularly vulnerable groups including young children and childbearing women), as well as various concerns with respect to the environment. Further measures and restrictions are therefore proposed on the use of lead ammunition. The HSE has called for comments on this proposal by 10<sup>th</sup> December.

Health and Safety Executive (2023). [UK REACH – public consultation on lead in ammunition](#).

#### ...call for comments on prosulfuron and pydiflumetofen

The HSE has launched open consultations on the active substances prosulfuron (a herbicidal active substance used on maize and sweet corn) and pydiflumetofen (a fungicide used on cereals and oilseed rape) by the 18<sup>th</sup> and 29<sup>th</sup> of December 2023, respectively. Draft Assessment Reports (DARs) are available on the HSE website.

Health and Safety Executive (2023).

[Pesticide active substance consultation on Article 7 amendment for prosulfuron](#).

[New active substance – PPP NAS 004 – Pydiflumetofen](#).

#### COT statement on calcium, iron and niacin fortification levels in bread and flour

In 2022, the Department for Environment, Food and Rural Affairs (DEFRA) proposed increases to calcium, iron and niacin (vitamin B3) fortification levels in non-wholemeal wheat flour to 15% of their respective Nutrient Reference Values (NRVs). The COT has assessed the potential human health risks arising from this proposal and does not anticipate any resultant adverse effects in the general population.

Committee on Toxicity of Chemicals in Food, Consumer Products and the Environment (2023). [Statement on the guidance levels for the fortificants in the bread and flour regulations](#).



## ACNFP discussion paper on dried miracle berry

At its most recent meeting, the ACNFP released a discussion paper on “dried miracle berry” (the dried fruit of *Synsepalum dulcificum*), used to increase the palatability of sour foods. The available document includes its composition, nutritional and toxicological information.

The Advisory Committee on Novel Food & Processes (2023). 163<sup>rd</sup> ACNFP Meeting 15<sup>th</sup> November 2023. [Dried Miracle Berry \(DMB\) Additional information discussion paper. ACNFP/163/01.](#)

## United States

### TCEQ issues a draft DSD on carbon tetrachloride

TCEQ has released a draft Development Support Document (DSD) on carbon tetrachloride, which summarises how chemical-specific toxicity values were derived for the general population. It established an acute 1-hour Reference Value (ReV) of 440 ppb (2800 µg/m<sup>3</sup>) and an acute 24-hour ReV of 83 ppb (520 µg/m<sup>3</sup>), based on the observed effects on the central nervous system of healthy volunteers following inhalation. Significant fatty changes in the liver of male rats exposed by inhalation for 2 years were the basis for a chronic ReV of 25 ppb (160 µg/m<sup>3</sup>).

Texas Commission on Environmental Quality (2023). [Carbon tetrachloride. CAS Registry Number: 56-23-5. Development Support Document. Draft.](#)

### US EPA IRIS review on inorganic arsenic

The US EPA has released a draft IRIS review on inorganic arsenic, which summarises the key scientific issues and establishes new toxicological reference values. In humans, the evidence demonstrates that inorganic arsenic causes diseases of the circulatory system (including ischemic heart disease) and diabetes. It is also considered likely to adversely affect pregnancy and birth outcomes and cause neurodevelopmental effects. The classification of arsenic as carcinogenic to humans has been retained by the US EPA, which derived a Cancer Slope Factor (CSF) of  $5.3 \times 10^{-2}$  for combined cancer risk (bladder and lung), as well as an overall oral Reference Dose (RfD) of 0.031 µg/kg bw/day based on increased incidences of cardiovascular disease.

US Environmental Protection Agency (2023). [IRIS Toxicological review of inorganic arsenic \[CASRN 7440-38-2\]. External Review Draft. EPA/635/R-23/166a.](#)

## Australia and New Zealand

### FSANZ risk assessments on three substances

FSANZ has released supporting documents for the risk assessments of a oligosaccharide and two enzymes:

- 2'-fucosyllactose from Genetically Modified (GM) *Escherichia coli* K-12
- beta-fructofuranosidase from GM *Trichoderma reesei*
- transglutaminase from GM *Bacillus licheniformis*

All three substances were considered safe under the proposed conditions of use in food. An oral Acceptable Daily Intake (ADI) of "not specified" was considered appropriate for the enzymes beta-fructofuranosidase and transglutaminase in the absence of any identifiable hazards.

Food Standards Australia New Zealand (2023). Risk and technical assessments. [A1277](#), [A1278](#) and [A1275](#).

## Canada

### Health Canada draft assessment on titanium-containing substances

Health Canada and Environment and Climate Change Canada have released a screening assessment discussing the human health and environmental effects of the titanium-containing substances group.

It was concluded that none of the chemicals met any of the section 64 criteria of the Canadian Environmental Protection Act (CEPA), which defines a compound as "toxic" in terms of its risk to human health or the environment.

Health Canada and Environment and Climate Change Canada (2023). [Draft Assessment: Titanium-containing substances group](#).

**Cover image:** Christmas wreath.

**See also:** Our article on page 7 relating to an FAO/WHO report on food allergens, including pine nuts. These are sourced from pine trees/pine cones, which are often used to make Christmas wreaths.

**Further information:** The toxicologists at bibra are experts at assessing allergenicity data.



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