NEWSLETTER JUNE 2021

REACH REGULATION

Unclaimed NONS (Notification of New Substances)

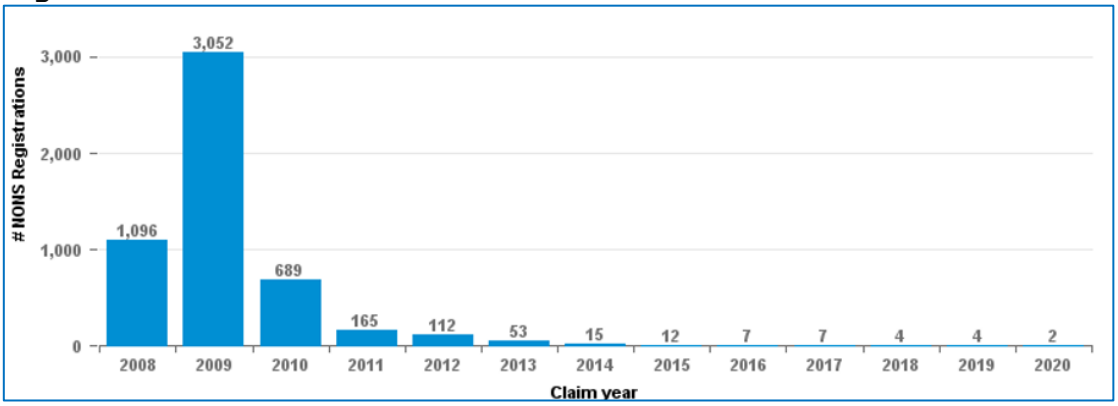
As you all know **NONS** (Notification of New Substances) was the procedure to "*register*", better notify, chemical substances to EU Member States before the advent of the REACH regulation (EC n. 1907/2006) and following EC Directive 67/548 and following amendments. Existing NONS were requested to be transferred to the new REACH system by applying the Art. 24 of the new regulation. With such procedure the old dossiers (done by DES software) were transferred into the new REACH regulation by companies using the experimental data and information already mentioned in such dossiers.

As mentioned in ECHA's latest 5-yearly report on the operations of REACH and CLP, there are several issues with NONS registrations:

- **92%** of them do not cover the standard information requirements according to REACH Reg. Indeed, REACH foresees that dossiers complying with the standard information requirements need to be submitted to ECHA only when NONS registrations are updated to increase the tonnage band, which so far happened for 8% of NONS registrations. This issue will remain unless the legal text is changed.
- **68%** of them are not in joint submissions and not updated. Issues arise when new registrants take the lead registrant role in REACH-IT and create a joint submission. After that, NONS registrants cannot update their NONS registration anymore without first joining the joint submission.
- **48%** of them are "unclaimed NONS", i.e. NONS notifications for which no company claimed ownership after they became registrations under REACH. These unclaimed NONS impose, therefore, some action to better comply with REACH

Over the past 12 years, **5.225 NONS** registration numbers were claimed by their owners, thereby confirming them as registrations under REACH. After the initial peak of NONS claiming in 2008-2010, NONS registration numbers are currently being claimed at a rate of about 4 per year with **4.739 NONS registration numbers still unclaimed** (see following Figure)

Figure n. 1



Considering that companies have had extensive time to claim the NONS registration numbers assigned by ECHA in 2008, and the diminishing returns on the NONS claiming in the past years, ECHA will put an end to this process in 2022.

To ensure that companies' expectations of being able to confirm ownership of NONS registration numbers are duly respected, ECHA will launch a campaign informing companies of the end of the NONS claiming period and will provide an **additional 6-month period** for completing the process of claiming any outstanding NONS registration numbers. For notifiers of unclaimed NONS only postal contact details from 2007 are available, and hence the campaign will focus on raising awareness via the ECHA website.

After the 6-month period, ECHA will remove the possibility to confirm ownership of unclaimed NONS registration numbers.

At the same time, the NONS registration numbers for which the assignment process has not been completed – i.e. numbers that have been created by ECHA but have not been claimed by the NONS notifiers – will be marked accordingly in ECHA's IT systems. Such a change in status will inform that the registration number was left unclaimed, and **no legal entity is associated with that registration.**

ECHA plans to communicate on its website in Q3-4 2021 about ending the NONS claiming period and the consequences for the unclaimed NONS. After a 6-month period for companies to claim any remaining NONS – or inform ECHA which ones they intend to claim but are having technical difficulties with – ECHA will close the process and change the status of the registration numbers that had not been confirmed by any former notifier, in 2022.

Afterwards, the NONS claiming module will be removed from REACH-IT and support material will be updated accordingly.

Companies needs to check and react accordingly!

Chromium Trioxide widely used in plating and surface treatment.

ECHA has received over 1.000 notifications from industrial sites using chromium trioxide in chrome plating and surface treatment in the EU. This follows two European Commission decisions in December 2020 granting authorisation to use the chemical until September 2024. Enforcement authorities can now carry out inspections as necessary.

REACH allows companies to apply for an authorization to continue or start using and placing chemicals included in the Authorization List on the market for a limited time. The authorization, granted by the European Commission, can cover the uses of the applying company but also their customers (downstream users). Those companies that use a chemical based on an authorization granted to an applicant up the supply chain, have to notify their use to ECHA within three months of the first delivery of the chemical taking place after the authorization decision.

The European Commission granted authorizations for five uses of chromium trioxide in December 2020, including functional chrome plating and surface treatment. The current authorizations expire in September 2024, but authorization holders can re-apply by submitting a review report to ECHA by March 2023.

Chrome plating and surface treatment are done in industrial settings, exposing workers to the harmful chemical that can cause cancer. These uses add a protective coating to metal parts and products and enhance the strength of the surface as well as wear and corrosion resistance. The treated surface does not contain chromium trioxide.

Notifications from 1.026 sites across Europe submitted by May 2021 confirm that chromium trioxide is still widely used in functional or hard chrome plating and surface treatment. The annual usage is estimated to be **7.000 tonnes**. The substance of very high concern was placed on the Authorization List in 2013 and its use has needed a specific authorisation in the EU since 2017.

By notifying the uses to ECHA, companies confirm that they follow the conditions for use set in the authorisation decisions granted to their suppliers. As part of the conditions, they must inform ECHA by the end of 2021 how their workers are exposed to chromium trioxide. This information will help companies to protect their workers even better by minimising their exposure to the carcinogen.

Given the increase in the number of notifications, ECHA has updated its downstream user notifications web page. It now contains searchable, public information from over **3.000 notifications** covering 14 substances in total.

New OECD test guideline on skin sensitisation

A new type of test guideline helps to reduce animal testing for chemicals by combining different data sources to improve test results for skin sensitisation using alternative test methods.
The guideline is the first to **include advice on computer predictions with tools such as the QSAR Toolbox**, a software co-developed by ECHA and the OECD. The guideline has been developed in a joint effort between the OECD, the EU's Joint Research Centre, national governments and ECHA. ECHA is also working on a related guidance for registrants and will publish it after this summer.

Dossier evaluation: request for a combination study at Annex VII

ECHA's Member State Committee has agreed to request a combined Comet assay (OECD TG 489) and Micronucleus test - MNO (OECD TG 474) for substances registered above one tonne per year under Annex VII to REACH.

The combination study will be requested if there is:

- *a positive Ames test – which checks the potential of chemicals to create mutations in bacteria;*
- *an indication of a chromosomal aberration concern; and*
- *no other adequate and appropriate in vivo genotoxicity data available in the dossier.*

This approach already applies to compliance checks and testing proposal examinations to fulfil information requirements for higher tonnage bands under REACH annexes VIII, IX and X. From thi moment on, registrants can expect requests for a combination study also for Annex VII dossiers.

The combined study can help to reduce animal testing while providing useful information on the potential of substances to induce chromosomal aberrations or gene mutation in vivo.

Higher costs are expected to cover such end-points!

BIOCIDES

Commission reports on the implementation of the Biocidal Products Regulation

The European Commission has published a five-year report and a staff working document on the implementation the Biocidal Products Regulation (BPR). It covers the period from 1 September 2013, when the BPR started to apply, until 31 December 2019. The report is mostly based on information gathered by EU countries.

EUROPEAN
COMMISSION

Brussels, 7.6.2021
COM(2021) 287 final

REPORT FROM THE COMMISSION TO THE EUROPEAN PARLIAMENT AND THE COUNCIL

on the implementation of Regulation (EU) No 528/2012 of the European Parliament and of the Council concerning the making available on the market and use of biocidal products

{SWD(2021) 128 final}

Conclusions (from the paper)

Eight years after the adoption of the BPR, all provisions are fully operational. The importance of biocides, notably of disinfectants for human hygiene and surface disinfection, was particularly highlighted during the COVID-19 pandemic. The use of the derogation provisions in place under the BPR to react to emergency situations allowed to address the severe shortages in the supply of disinfectants following the steep increase in the demand. The concerted efforts of industry, Member States and the Commission allowed to address the unprecedented situation created by the COVID-19 pandemic.

*The main problems identified in this report are the **slow progress with the evaluation of active substances** included in the Review Programme and the continuous substantial delays in both active substance approval and product authorisation processes. The slow progress with the evaluation of the active substances in the Review Programme, already identifiedunder the BPD, continued after the entry into application of the BPR. Thus, 5 years before the twice extended deadline of 31 December 2024, **only 35% of the work programme has been completed**.*

Very limited innovation on new active substances occurred under the BPR. According to stakeholders, innovation is hindered by high regulatory costs and very long procedures, the relatively small market for biocides and its fragmentation, and the small returns on investment.

The slow progress with the Review Programme has been a further disincentive for developing new active substances, since products containing active substances in the Review Programme and still under evaluation can be made available on the market under national rules without having to respect restrictions put in place under the BPR to protect health and environment. Public investment into research could help to increase innovation in this area.

***The completion of the Review Programme is thus crucial** for the achievement of the objectives of the BPR. The longer the completion of the work programme is delayed, the longer biocidal products containing active substances not yet evaluated for safety and efficacy may be made available on the market. It is therefore imperative to accelerate the pace of the evaluation of existing active substances and complete the Review Programme as soon as possible.*
*In addition, the Commission receives an increasing number of correspondence from companies, who cannot find an evaluating Member State for the approval or renewal of approval of active substances or for the authorisation of biocidal products (either as reference Member State for mutual recognition or evaluating Member State for Union authorisation), as all Member States approached refuse to do so. The main reason for all delays observed – and the difficulties for companies finding reference or evaluating Member States accepting applications – **is a systemic lack of resources in the Member States**.*

The Commission therefore calls on Member States to ensure that Competent Authorities have the appropriate resources to fulfil all their obligations under the BPR within the applicable deadlines. The Commission invites Member States to review the situation of the fees collected for BPR procedures, with regard to the appropriateness of their level and the potential need to ring-fence the revenue derived from them for activities related to the BPR.

The Commission will also launch a call to set up a contract for providing Member States' Competent Authorities specific technical support to complete their evaluations. A full evaluation of the BPR, planned for 2025, will analyse in-depth the fitness of the current regulatory framework as a basis for deciding on the need for further action.

If Member States do not take the necessary measures to ensure that their authorities can execute the role of evaluating authority for applications for approvals, authorisations and renewals, the regulatory system set out in the BPR cannot function properly.

Glyphosate: EU regulators begin review of renewal assessments

ECHA and the European Food Safety Authority (EFSA) have received a draft assessment of glyphosate carried out by four EU Member States and will now begin to consider the findings. Glyphosate – the most widely used herbicide in the world – is currently authorized for use in the EU until December 2022.

Glyphosate is a chemical that is widely used in plant protection products (PPPs). Glyphosate-based PPPs – i.e. formulations containing glyphosate, co-formulants and other chemicals – are mainly used in agriculture and horticulture to control weeds that compete with cultivated crops.

The European Commission granted **a five-year approval for glyphosate in 2017**. It is currently approved for use in the EU until 15 December 2022. This means it can be used as an active substance in PPPs until that date, subject to each product being authorized by national authorities following a safety evaluation.

National authorities of France, Hungary, the Netherlands and Sweden – known as the Assessment Group of Glyphosate (AGG) – have examined all the evidence submitted by the companies that are seeking renewed approval to market the substance in the EU. The AGG's draft report runs to around 11.000 pages.

ECHA and EFSA will now organize parallel consultations on the draft report. These will be open to the public and launched in the first week of September this year.

The consultations are the first step in the assessments. ECHA's Committee for Risk Assessment (RAC) will review the classification of glyphosate under the Classification, Labelling and Packaging (CLP) Regulation. Classification of chemicals is based solely on the hazardous properties of a substance and does not take account of the likelihood of exposure to the substance. Exposure is considered as part of the risk assessment process led by EFSA.

Glyphosate currently has a harmonized classification as causing serious eye damage and as toxic to aquatic life with long-lasting effects, prior to and following the assessment by ECHA in 2017. No classification for germ cell mutagenicity, carcinogenicity or reproductive toxicity was warranted. The current proposal from the four Member States does not foresee a change to the existing classification.

Once ECHA has adopted its opinion on the classification of glyphosate, EFSA will finalise its peer review and publish its conclusions, expected in late 2022. Based on this risk assessment, the European Commission will decide whether or not to renew glyphosate.

PHARMA

Nitrosamine in drug products: an open discussion

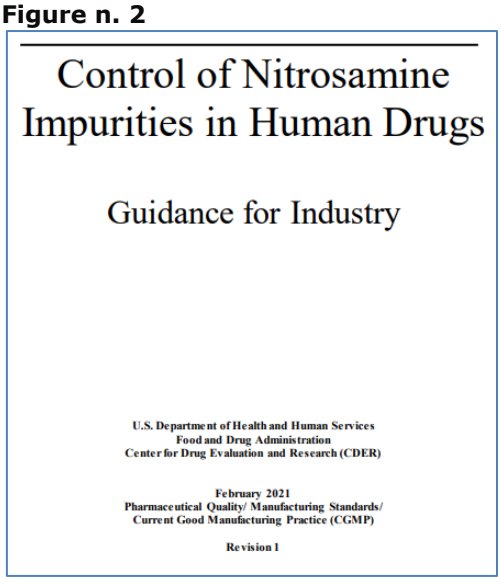
Nitrosamines have become a focus of global regulatory agencies, including FDA, due to the discovery of trace amounts of these compounds in a class of drugs known as angiotensin II receptor blockers (ARB), frequently referred to as "sartans." The "sartan" molecules involved include valsartan, losartan, irbesartan, azilsartan, olmesartan, eprosartan, candesartan, and telmisartan. Valsartan and losartan were the most severely affected due to their market share when several lots were recalled.

The genotoxic and carcinogenic potential of N-nitrosamines raises a serious safety concern, and in September 2020, the FDA issued guidance for the pharmaceutical industry regarding the control of nitrosamines in drug products. The FDA database shows that >1400 product lots have been recalled from the market due to the presence of carcinogenic N-nitrosamine impurities at levels beyond the acceptable intake limit of 26.5 ng/day. The drugs that were present in recalled products include valsartan, irbesartan, losartan, metformin, ranitidine, and nizatidine. This perspective provides a critical account of these product recalls with an emphasis on the source and mechanism for the formation of N-nitrosamines in these products.

Many of the global regulatory authorities, including WHO, EMA and Health Canada have provided directives regarding evaluation of nitrosamines in products including complete retrospective analysis of all approved Drug Products (DPs) based on the strong concern of possible carcinogenicity effects on exposed patients and to mitigate such an effect.

Very recently, in February 2021, FDA release a draft guidance for Industry as shown in the next figure.

Figure n. 2


Control of Nitrosamine Impurities in Human Drugs

Guidance for Industry

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)

February 2021
Pharmaceutical Quality/ Manufacturing Standards/
Current Good Manufacturing Practice (CGMP)

Revision 1

The FDA Guidance for Industry gives suggestion to the industry on how to approach the assessment of the nitrosamine in drug active and drug products including some indication of acceptable limits for some of them as in the following figure:

Figure n. 3

Table 1. AI Limits for NDMA, NDEA, NMBA, NMPA, NIPEA, and NDIPA in Drug Products

Nitrosamine	AI Limit (ng/day)[1,2]
NDMA	96
NDEA	26.5
NMBA	96
NMPA	26.5
NIPEA	26.5
NDIPA	26.5

[1] The AI limit is a daily exposure to a compound such as NDMA, NDEA, NMBA,NMPA, NIPEA, or NDIPA that approximates a 1:100,000 cancer risk after 70 years of exposure. Appendix B includes a description of the AI derivation for NDMA, which is an example of how FDA applied ICH M7(R1) to set a limit.
[2] The conversion of AI limit into ppm varies by product and is calculated based on a drug's maximum daily dose (MDD) as reflected in the drug label (ppm = AI (ng)/MDD (mg)).

Recommendation to API manufactures and to Drug Products manufacturers are included to mitigate the impact of nitrosamine impurities in drugs as well as how to control the drug supply chain and how to report changes to reduce their presence.
Since some years, Pharmaceutical Industry activated itself to study such a problem from an analytical point of view and provide toxicological assessment to reach possible acceptable level of nitrosamine species in a variety of drug product.
The industry proposes a streamlined approach to reduce the presence of nitrosamines in their Drug Products is based on better understanding of the source of these impurities. The risk evaluation will take into account all aspects of the development of the DPs throughout its life cycle.

Five sources of nitrosamines formation have been identified:

- presence of certain process condition and certain raw materials, starting material and intermediates with lack of complete purging methods to avoid the contamination;

- the use of sodium nitrite or other nitrites in presence of secondary and tertiary amines. They can be present in solvent and reagents or in common bass such as triethylamine;

- the use of contaminated raw materials such us in the manufacturing process such as recycled solvents, reagents and catalyst that can pose a risk due to the presence of amines in the waste stream;

- Using third parties to recover the materials (again solvents, reagents and catalysts) which are not addressed to pose attention to the contamination matter and do not use appropriate dedicated equipment;

- the use of contaminated starting materials including intermediates from providers using chemical processes which produce nitrosamines.

The risk-based approach adopted by pharmaceutical industry is addressed to understand the chemical source of nitrosamines by evaluating the chemical process to manufacture the API (Active Pharmaceutical Ingredients) and any possible co-formulants.

This implies several focused evaluations:
- a complete analysis of the supply chain/s;
- a complete analysis of the chemical manufacturing processes;
- a complete evaluation of the Drug Product, its storage condition, and possible degradation products and consequent reaction products when approaching the nitrosamine contamination in the final DP;
- the development of suitable analytical methods to detect nitrosamines species with determination of a suitable LOD (Limit of Detection) and LOQ (Limit of Quantification) in correlation with the acceptable limits or absence of nitrosamine in API and DPs.

The discussion at the scientific and regulatory level is never-ending with particular reference to the setting of suitable analytical methods and to understand the huge chemical processes and cross-formation processes which lead to nitrosamines presence and, of course, setting of related acceptable limits.

As usual……more science is still needed!

EVENTS

End of the newsletter