Nitrosamines in Medicines - What are the issues?

Introduction

The term “Nitrosamines” is used to designate a vast group of N-nitroso compounds (NOCs), bearing an N–N=O side arm (Figure 1). Nitrosamines are formed by a reaction between nitrates or nitrites and certain amines both exogenously and endogenously. This reaction can occur, for example, under the acidic pH conditions found in the mouth or stomach. Nitrosamines and/or their precursors are widely distributed in the environment and can also be found in diverse consumer products such as processed meats, alcoholic beverages, cosmetics, and cigarette smoke.

Figure 1. 3D structure of nitrosamine (H_2N_2O)

Concerns over the safety of nitrosamines are not new despite their presence in consumer products. Many have potent biological activity and more than 90% of known nitrosamines are considered to be carcinogens spanning several orders of magnitude of potency. They are known to cause cancer in a number of animal species, in multiple organs, by different routes of administration. In addition, the same nitrosamine can cause different tumours in different animal species and have different latencies following short, including a single dose, and long durations of exposure. Several nitrosamines are classified as human carcinogens.

The discovery of nitrosamines in a widely prescribed medicinal drug class in 2018 raised concerns for patient safety and the need for regulatory action. However, it should be noted that there is a very low risk that nitrosamine impurities at the levels found in medicines could cause cancer in humans.

Nitrosamine Impurities in Medicines (Figure 2)

The presence of the nitrosamine *N*-nitroso-dimethylamine (NDMA), as a contaminant in the drug valsartan[1], was first reported in June 2018. Subsequently, an EU referral procedure[2] was undertaken to assess the impact of this impurity on the benefit-risk of valsartan-containing medicines https://www.ema.europa.eu/en/human-regulatory/post-authorisation/referral-procedures). The referral was quickly extended to cover all sartan medicines containing a tetrazole ring as part of their structure (see European Medicines Agency, 2020a). Two nitrosamines received particular attention, namely NDMA and *N*-nitrosodiethylamine (NDEA).

Concerns regarding nitrosamine contaminants in certain medicinal products compelled the Regulatory Authorities to take steps, including drug withdrawals from the market and provision of online advice to prescribers and patients. Similar activities have taken place in the USA, Canada, Switzerland, Japan, Singapore and Brazil, as well as the World Health Organisation

In July 2018, the USA Center for Drug Evaluation and Research (CDER), activated the CDER Nitrosamine Task Force (NTF) to manage the contamination incident, under the direction of the CDER Office of Counter Terrorism and Emergency Coordination (CTECS).

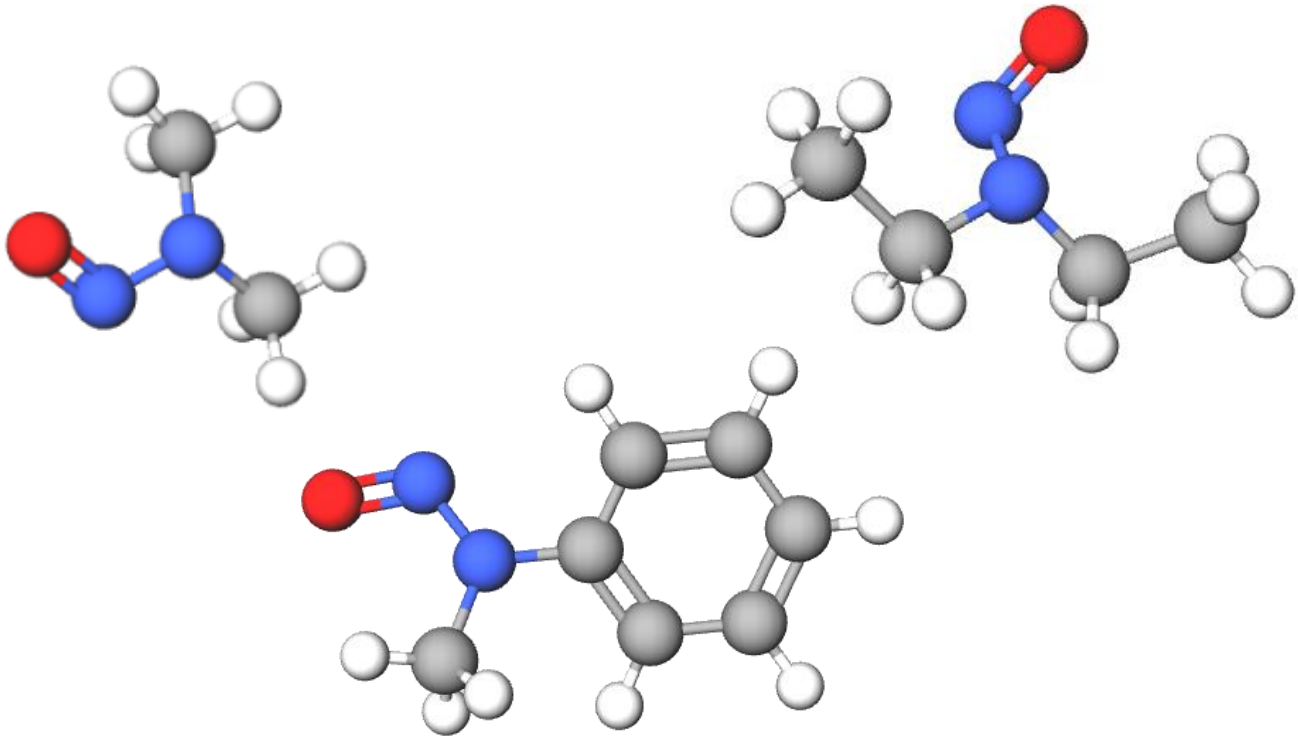

Figure 2. 3D structure of nitrosamines. Top right: N-nitroso-dimethylamine (NDMA). Top left: N-nitrosodiethylamine (NDEA). Bottom: N-nitrosomethylphenylamine (NMPA)

In 2019, the European Medicines Agency undertook a review of the drug ranitidine, a medicine used to reduce stomach acid, in light of concerns over the identification of the presence of NDMA and its potential endogenous formation in gastric-like conditions. This review led to the suspension of the Marketing Licences of all ranitidine-containing medicinal products in the EU in 2020 (see European Medicines Agency, 2020b), which is why this medicine is no longer available as a medicinal product.

More recently, a general EU review procedure (see European Medicines Agency, 2020c) on the presence of nitrosamines in human medicines to investigate the potential risk of nitrosamines in manufacturing of medicines has been initiated. To date, the following nitrosamines have been reported as impurities in medicines: NDMA, NDEA, *N*-nitrosomethylphenylamine (NMPA), *N*-nitrosodiisopropylamine (NDIPA), 3*N*-nitrosoisopropylethylamine (NIPEA), nitrosodibutylamine (NDBA), and *N*-nitroso-*N*-methyl-4-aminobutyric acid (NMBA).

Where Do the Impurities Come From

The main sources of contamination were identified as changes in the manufacturing process, which involved combinations of amines and nitrogen compounds and the use of specific catalysts and reagents. There are also examples of nitrosamine formation during the process of medicine packaging. The use of contaminated reagents or solvents has also been associated with the presence of nitrosamines in medicines. Other factors include stability, excipients and storage conditions

Current role of Regulatory Authorities in reviewing Nitrosamine Impurities in medicinal products

In order to assess any allowed presence of nitrosamines in medicines Regulatory Authorities worldwide have been faced with a number of issues as there is a lack of robust toxicological data on some of the nitrosamines. Also, there is a considerable gap in the knowledge as to whether endogenous formation of the nitrosamines exceeds, is equal to, or is less than, the levels detected in medicines. This knowledge gap has led to criticism in some public sectors that there has been an overreaction by Regulatory Authorities as shown by the withdrawal of some medicines due to concerns as described above. However, irrespective of the risk of endogenous exposure, Regulatory Authorities felt that exogenous nitrosamines, *i.e.* those not from the environment, posed an additional human safety risk, and it was this increase in risk that had to be investigated.

Thus, subsequent to the general EU review procedure mentioned above, conservative methods have been recommended to set limits for nitrosamines in new medicinal products by the EU's Safety Working Party (SWP) (European Medicines Agency, 2020c). In addition, the European Medicines Agency and US Food and Drug Administration have now set daily intake limits for nitrosamines in new

medicines (Food and Drug Administration, 2020, European Medicines Agency 2021). If batches of an approved medicine are shown to contain levels of nitrosamines above the allowable daily intake limits, it is recommended that they are recalled to prevent patient use. However, in some cases, potential withdrawal of affected medicines may not be in the interest of patients because of the lack of alternative medicines and patients can be advised to continue taking their medicines as directed. A benefit: risk to the patient is considered very carefully in these cases.

In addition to the recommendations on setting limits, Regulatory Authorities have provided to drug companies guidance on strategies to mitigate the presence of nitrosamines in human medicinal products. These include careful design of manufacturing processes to avoid nitrosamine formation, risk assessments for processes and raw materials, and implementation of appropriate control strategies. Further guidance has been provided on calculating limits when multiple nitrosamines are present and on aspects of analytical methods for detection and quantification of nitrosamines at trace levels.

For the future, Regulatory Authorities will continue to monitor the issue of nitrosamine contamination and provide updated information on their websites.

References

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Footnotes

1 Valsartan is a medicine used to treat high blood pressure

2 a procedure used to resolve issues such as concerns over the safety or benefit-risk balance of a medicine or a class of medicines