Nitrosamines

From Valsartan to Metformin – notorious impurities in drug products

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Abstract

Since June 2018, various N-nitrosamines have been detected worldwide in active pharmaceutical ingredients (API) of multiple manufacturers. Two referral procedures were started in the EU, referring to sartans (July 2018) and to ranitidine (Sept 2019).
N-nitrosamines are classified as probably carcinogenic to humans. Strict interim limits up to less than 1 ppm in the API have been established. This will be lowered to 30 ppb after a transitional period of 2 years. These limits represent a major challenge for the current technical state of ultra-trace analytics. Analytical methods must be a) highly sensitive to achieve reliable and reproducible detection of the analyte in the lower to middle ppb range and b) highly selective to enable precise determination in the presence of high amounts of matrix. Eligible methods include either liquid or gas chromatography coupled with a mass spectrometer.
Due to the multitude and diversity of nitrosamines, it is impossible to develop one screening method that covers all of them, especially in the ultra-trace range. Therefore, each method must not only be specifically tailored to the API and its "own" set of N-nitrosamines, but also validated for each testing laboratory, the API and the change in composition.
By 26 Mar 2020, the manufacture of all medicinal products containing chemically synthesized API must be reviewed in detail to identify any risk of potential nitrosamines formation. All products at risk must be tested in order of priority. To ensure nitrosamine-free medicinal products, the marketing authorization holder (MAH) must implement appropriate control strategies and changes of the manufacturing process until Sept 2022.

Zusammenfassung

Nitrosamine: Von Valsartan bis Metformin – altbekannte Verunreinigungen in Arzneimitteln
Seit Juni 2018 wurden weltweit verschiedene N-Nitrosamine in pharmazeutischen Wirkstoffen mehrerer Hersteller nachgewiesen. In der Folge wurden zwei EU-weite Überprüfungsverfahren (Referral) zu Sartanen (Juli 2018) und Ranitidin (Sept 2019) eingeleitet.
N-Nitrosamine werden als wahrscheinlich krebserregend für den Menschen eingestuft. Vorläufig wurden strenge Grenzwerte in Wirkstoffen festgelegt, teilweise unterhalb von 1 ppm. Nach einer Übergangszeit von 2 Jahren werden diese Grenzwerte noch einmal deutlich auf 30 ppb verschärft werden. Für den derzeitigen Stand der Technik in der Ultraspurenanalytik stellen diese Grenzwerte eine enorme Herausforderung dar. Analytische Methoden müssen a) hochsensitiv sein, um die Analyte im unteren bis mittleren ppb-Bereich verlässlich und reproduzierbar nachweisen zu können und b) hochselektiv sein, um auch geringste Mengen eindeutig in Arzneimitteln mit einem hohen Matrixanteil bestimmen zu können. Als geeignete Analysenmethoden haben sich hier die Flüssigkeits- und Gaschromatographie gekoppelt mit der Massenspektrometrie (LC-MS, GC-MS) erwiesen. Aufgrund der Vielzahl und Diversität von Nitrosaminen ist es unmöglich, eine einzige Screening-Methode zu entwickeln, die alle diese Substanzen – insbesondere im Ultraspurenbereich – abdeckt. Vielmehr muss jede Analysenmethode nicht nur speziell auf den Wirkstoff und die potenziell darin enthaltenen N-Nitrosamine zugeschnitten werden, sondern auch für jedes Untersuchungslabor, für jeden Wirkstoff und für jede Matrix validiert werden.
Bis zum 26. März 2020 müssen die Herstellverfahren aller Arzneimittel mit chemisch synthetisierten Wirkstoffen detailliert auf das Risiko einer potenziellen Nitrosamin-Verunreinigung geprüft werden. Alle gefährdeten Arzneimittel müssen anschließend analytisch auf Nitrosamine getestet werden, Produkte mit einem hohen Risiko sollen hierbei priorisiert werden. Um die Abwesenheit von Nitrosaminen zu gewährleisten, müssen Zulassungsinhaber weiterhin bis Sept 2022 geeignete Kontrollstrategien und Änderungen des Herstellungsprozesses implementieren.

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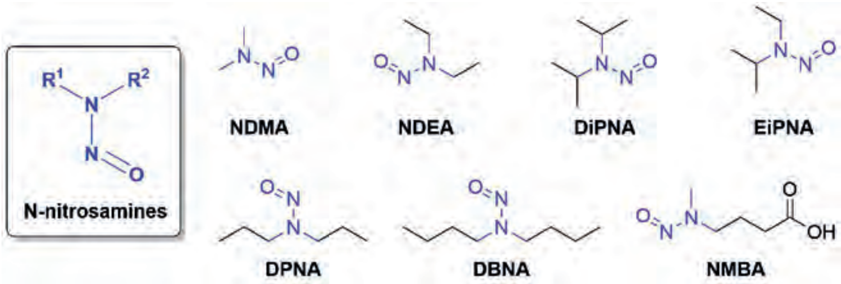

Figure 1: Structural formulas of N-nitrosamines detected in various APIs (source: all figures were made by the authors).

Nitrosamines (or more precisely N-nitrosamines) refer to the chemical structure of a nitroso group bonded to a secondary amine (structural formula refer to Fig. 1). In June 2018, the EU authorities were notified of a previously undetected impurity, N-nitrosodimethylamine (NDMA), in the active pharmaceutical ingredient (API) valsartan, an angiotensin-II-receptor blocker [1]. This analytical finding was the start of a series of nitrosamine findings in medicinal products and has developed to a global drug quality issue with continuously growing impact on the manufacturing processes of API and medicinal products.

On 5 July 2018, the *European Commission* (EC) started a referral under Article 31 of Directive 2001/83/EC for valsartan (procedure no. EMEA/H/A-31/1471) [1]. Subsequently, valsartan batches from almost all marketing authorization holders (MAH) were recalled from the international markets. Given the detection of another nitrosamine, N-nitrosodiethylamine (NDEA), in valsartan and sufficient reason to believe that the generation of nitrosamines took place in the synthesis step of the tetrazole ring formation, the *Committee for Medicinal Products for Human Use* (CHMP) decided on 20 Sept 2018 to widen the scope of the referral to include all sartans with a tetrazole moiety in their molecular structure [2]. Comprehensive investigations revealed the presence of further nitrosamines in various sartans (Fig. 1). Again, numerous recalls of sartan medicinal products on the global markets with partial drug shortage for several API were the consequences.

After conclusion of the sartan referral procedure with decision of the EC on 2 Apr 2019, nitrosamines were also detected in further API. On 26 Apr 2019, the *European Medicines Agency* (EMA) informed about the detection of low levels of NDMA in a few batches of pioglitazone [3]. Routine laboratory analysis by an US-American online pharmacy of the H2 (histamine-2)-receptor antagonist ranitidine revealed the presence of NDMA in levels beyond the acceptable threshold. Later, NDMA was also detected in the chemically similar API nizatidine. The EU authorities started a new referral procedure on 12 Sept 2019 for ranitidine (procedure no. EMEA/H/A-31/1491). Again, numerous ranitidine medicinal products were recalled worldwide [4]. For some generic ranitidine medicinal products, the indication Zollinger-Ellison syndrome was temporarily suspended because the NDMA intake at lifelong high-dose ranitidine therapy would exceed the acceptable daily intake limit [5]. As of the editorial deadline of this publication, it was announced that NDMA has been found in a few batches of the antidiabetic drug metformin [6, 7].

NDMA and NDEA are genotoxic and carcinogenic agents in animals and are classified as probably carcinogenic to humans (class 2A carcinogens) by the *International Agency for Research on Cancer*. Two-step metabolic activation of nitrosamines in humans is hypothesised with initial cytochrome P450-mediated α-hydroxylation finally leading to a diazonium ion which can form mutagenic DNA-adducts. In rats and monkeys, the primary targeted organ is the liver; however, valid data for target organ(s) of oral NDMA or NDEA exposure of humans are not available [8]. For medicinal products, the *International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use* (ICH) guideline M7 sets out principles for determining acceptable limits for mutagenic impurities. N-nitroso-compounds are compounds with an extremely high carcinogenic potency which are part of the so-called "cohort of concern". For such compounds, acceptable limits need to be derived from compound-specific carcinogenicity data, as the concept of Threshold of Toxicological Concern (TTC), where the intake of 1.5 µg of the impurity per day is considered to be of an acceptable risk, is not considered applicable [9]. In conclusion of the sartan referral, strict interim compound-specific acceptable levels were established for the so far detected nitrosamines. An acceptable intake level was defined as the dose resulting in an increased cancer risk of 1:100,000 in an individual with lifetime exposure to the impurity [9]. For NDEA, DIPNA (N-nitrosodiisopropylamine) and EIPNA (N-nitrosoethylisopropylamine), the limit was set to 26.5 ng per day; the limit for NDMA and NMBA (N-nitroso-n-methyl-4-aminobutyric acid) was set to 96.0 ng per day [8, 10]. As these limits correlate with the daily administered amount of an API, the thresholds for the nitrosamines vary depending on the respective maximum recommended daily dose. Applying this principle to the toxicological evaluation of NDMA in ranitidine and metformin according to the recommendations of the *Co-ordination Group for Mutual Recognition and Decentralised Procedures – Human* (CMDh) [11] results in


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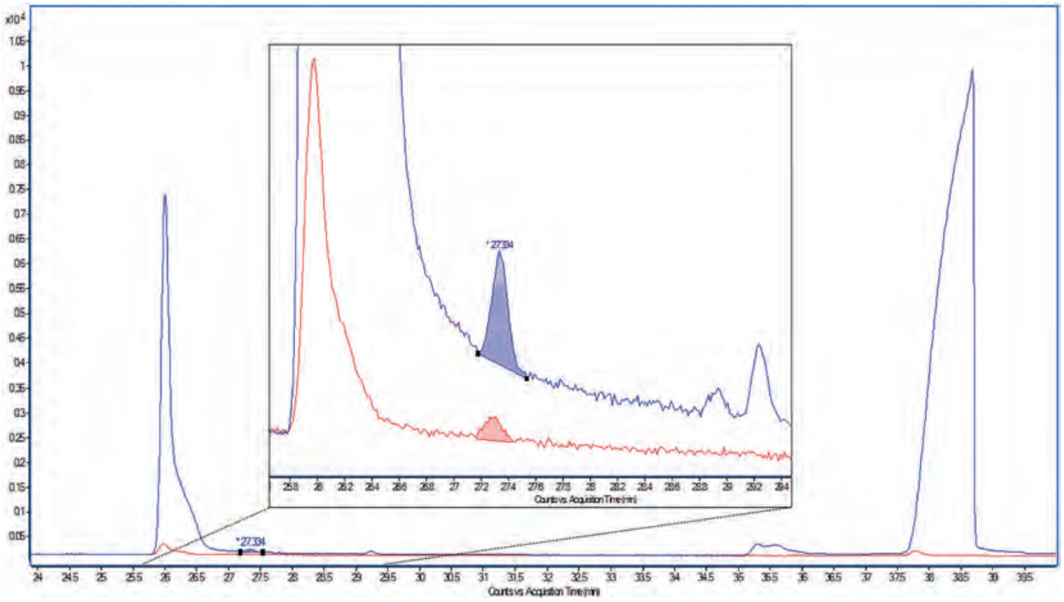

Figure 2: GC-MS chromatogram depicting a NDMA solution (LOD, red) and a candesartan solution spiked with 0.03 ppm NDMA (LOQ, blue).

thresholds of 0.106 ppm and 0.032 ppm (Table 1). After a transitional period of 2 years (until Apr 2021), pharmaceutical companies will have to demonstrate that their sartan substances are free from nitrosamines (technically feasible limit of quantification 0.03 ppm) [10].

The European Pharmacopoeia (Ph. Eur.) monographs for the respective sartans were revised and the transitional limits were included (publication in the 10th edition of the Ph. Eur., implementation date: 1 Jan 2020) [12].

Besides API synthesis, packaging materials have been identified as potential nitrosamines source. Nitrosamine contamination has been observed by one MAH in finished products stored in blisters (presumption that lidding foil containing nitrocellulose printing primer may react with amines in printing ink to generate nitrosamines) [11]. In an U.S. Pharmacopeia (USP) Stimuli article on elastomers in inhalation packaging / delivery systems, the potential reaction between secondary amines formed from vulcanization accelerators such as thiurams and dithiocarbamates and nitrosating agents to various nitrosamines is issued. It has been proposed to amend additional tests and acceptance criteria for six volatile nitrosamines in the USP chapter 381: 1 ppb for N-nitrosodibutylamine (NDBA), NDEA, NDMA, N-nitrosopiperidine (NPIP) and N-nitrosopyrrolidine (NPYR) each, 5 ppb for N-nitrosomorpholine (NMOR) and 10 ppb for N-nitrosamines in total [13].

Authorities have defined various thresholds for impurities in API and drug products in the guidelines ICH Q3A [14] and Q3B [15]. For a "classical" impurity, the lowest reporting level is set to 0.03 % for a maximum daily dose of 2 g, which corresponds to 300 ppm. For "critical" impurities, with an unknown or higher toxicity, harsher limits have been set. ICH Q3C [16] and Q3D [17] both require reporting levels in the ppm range for residual solvents or even in the ppb range for some elemental impurities. Even stricter limits apply to potentially genotoxic impurities (PGI), which are depicted in the ICH guideline M7 [9]. Applying the TTC concept to an API with a daily dose of 1.5 g per day would correspond to an acceptable limit of 1 ppm for the impurity. Critical impurities must therefore be detectable in the trace range or even ultra-trace range.

For the currently identified nitrosamines in medicinal products, by orders of magnitude lower acceptable interim limits have been established. For the time being, the authorities have set the limit of quantitation (LOQ) for nitrosamines in the API valsartan to 0.3 ppm and 0.08 ppm [18]. This will be lowered to 0.03 ppm (30 ppb) after a transitional period of 2 years [8]. The limit of quantitation describes the limit at which the difference between two distinct values can be reasonably discerned. If more than one nitrosamine is identified, regardless of the amount detected, the batch in question should be discarded. This requires that the limit of detection (LOD), at which the analyte signal is clearly distinguishable from the blank value, must be even lower (Fig. 2).

Therefore, analytical methods for the determination of nitrosamines must be highly sensitive to achieve reliable and reproducible detection of the analyte in the lower to middle ppb range. In addition, high selectiv-

■ **Table 1**

Interim limits for nitrosamines in sartans [10] and further API according to [11].

API	Max. daily dose [mg]	NDEA, DIPNA, EIPNA		NDMA, NMBA	
		Limit [ng/day]	Limit [ppm in API]	Limit [ng/day]	Limit [ppm in API]
Valsartan	320	26.5	0.082	96.0	0.300
Losartan	150	26.5	0.177	96.0	0.640
Olmesartan	40	26.5	0.663	96.0	2.400
Irbesartan	300	26.5	0.088	96.0	0.320
Candesartan	32	26.5	0.820	96.0	3.000
Ranitidine	900			96.0	0.106
Metformin	3000			96.0	0.032

ity is imperative as very low concentrations of the analyte must be determined in the presence of high amounts of matrix, e.g. in tablets. Common methods for the determination of PGI usually include either liquid (LC) or gas chromatography (GC) coupled with a mass spectrometer (MS), to achieve the required sensitivity.

Several methods were published by the *Official Medicines Control Laboratory* (OMCL) for the determination of N-nitrosamines in sartans and ranitidine, using both LC and GC systems [20]. Other federal agencies, like the *Food and Drug Administration* (FDA), have published their own methods for the determination of nitrosamines. For ranitidine, due to its degradation and the formation of NDMA *in situ* at high temperatures, the FDA recommends the use of LC-MS methods [21]. Since most N-nitrosamines are volatile substances with relatively low molecular masses, GC-MS offers a powerful alternative to LC-MS. The use of GC often results in narrower, more symmetrical peaks with significantly better resolution and greatly reduced matrix effects.

One of the earliest methods for the determination of nitrosamines in valsartan was published by the FDA in Nov 2018 [22]. It employs a GC-MS method and allows the detection of NDMA and NDEA in the API simultaneously. Interestingly, this method did not quite reach the limits of 0.03 ppm N-nitrosamines in the finished drug, which the FDA declared to be technically feasible. The amounts of NDMA and NDEA, that could be quantified by this method, were 0.05 and 0.03 ppm for the pure API and 0.08 and 0.04 ppm for the finished drug product respectively.

Since then, much research has been done to further lower the limit of quantification. Another example is a method by the *Swiss Agency for Therapeutic Products* (swissmedic), which mainly optimized two parameters: the injection volume and the injection mode [23]. By increasing the injection volume, more analyte reaches the detector, which in turn increases the signal-to-noise ratio and therefore the sensitivity to lower analyte concentrations. However, the higher injection volume also increases the risk of backflash: the applied sample volume exceeds the contents of the sample chamber upon evaporation, which is why only part of the analyte reaches the detector and the signal-to-noise ratio decreases again. To compensate for this effect, an increased pressure is applied during injection in pulsed splitless mode, which again reduces the volume of the gaseous sample in the sample chamber. These rather harsh conditions certainly shorten the service life of the columns used and increase the frequency and effort required for cleaning the entire GC system, but allowed the LOQ to be reduced to 0.03 ppm.

Even though there are now several methods available for the determination of nitrosamines, they have been developed and validated exclusively for specific analytes in specific API. Due to differing compositions, matrix effects pose the biggest challenge for this ultra-trace analysis, especially in the case of drugs with varying strengths. Since the limit values for PGI are calculated based on the contained API, significantly larger sample quantities must be weighed in for the analysis of low strengths to achieve the required sensitivity, resulting in significantly higher amounts of matrix. Therefore, sample preparation (while limiting solvents and sample volumes for GC) must be optimized very carefully while strictly avoiding contamination. As a result, methods need not only to be established for each testing laboratory, they need to be validated for each drug and each change in composition.

The biggest challenge – and one of the reasons why nitrosamines in sartans were not found before 2018 – remains: to distinguish signals in the ppm to ppb range from the baseline and to clearly identify a substance, the analytical chemist has to know what to look for beforehand (Fig. 2).

On 26 Sept 2019, all MAH of human medicinal products containing chemically synthesized API were requested to review their medicines for the possible presence of nitrosamines and to take the necessary measures to ensure nitrosamine-free medicinal products [24, 25]. As a first step, MAH are to assess the risk of nitrosamine formation during the manufacture of their medicinal products, from the synthesis of the API to the manufacture of the finished product and beyond, by assessing the risk of nitrosamine formation during storage throughout the shelf life [11]. The most common cause of nitrosamine formation is the simultaneous presence of secondary amines and nitrite or other nitrosating agents – usually under acidic conditions – during the synthesis. However, tertiary amines can also undergo nitrosation via more complex pathways; and tertiary amine bases are known to degrade to secondary amines. All starting materials, intermediates, reagents, solvents and catalysts of each synthetic step must be carefully examined for the potential presence of relevant amines or nitrosating agents. If carry over can occur, the same, previous and subsequent process steps should be considered. Because of the multitude and diversity of nitrosamines (Fig. 1), it is impossible to develop a screening method that covers all these substances, especially in the low ppb range.

The *International Pharmaceutical Excipients Council* (IPEC) Europe developed a questionnaire to facilitate gathering information about potential nitrosamine sources and to assist companies to prepare the required risk assessments [19]. Based on the experience from the referrals, a special attention should be paid to the use of recovered materials including recovery outsourced to third parties who are not aware of the content of the materials they are processing and routine recovery processes carried out in non-dedicated equipment, use of contaminated starting materials and intermediates supplied by vendors that uses processes or raw materials which allow nitrosamine formation, cross-contamination due to different processes run on the same line and due to inadequate phase separations as well as degradation processes of starting materials, intermediates and drug substances. Also nitrosamine contamination by the use of certain packaging materials must be considered [11, 13]. The MAH must submit the conclusions of the risk assessment for all their products until 26 Mar 2020 to the competent authorities.

In the second step, all products at risk must be tested in order of priority. If nitrosamines are detected in any of their medicines, MAH must inform authorities promptly so that appropriate regulatory actions can be taken. Appropriate templates for the notification of the outcome of the risk evaluation (step 1) and the confirmatory testing (step 2) are provided by the CMDh. If MAH identify that changes are necessary in their production process, their product formulation or in the control strategy and specifications to ensure nitrosamine-free medicinal products (step 3), they should liaise with competent authorities in order to evaluate the type of variation needed and submit one in a timely manner [11]. The overall review including the confirmatory testing of the products at risk as well as the necessary changes of the manufacturing processes with related variations for amendment of the quality dossier should be finalized until 26 Sept 2022 at the latest [24, 25].

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