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DETECTION OF NITROSAMINE IMPURITIES IN SARTAN DRUG PRODUCTS BY GC-MS

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1. INTRODUCTION

In July 2018 a manufacturer of valsartan active substance in China notified regulators that some batches contained N-nitrosodimethylamine (NDMA), and recalls of finished tablets followed in many countries [1, 2]. Further sartans, including losartan and irbesartan, were then found to carry other nitrosamines such as N-nitrosodiethylamine (NDEA) and N-nitroso-N-methyl-4-aminobutyric acid (NMBA) [1, 3]. Sartans are angiotensin II receptor blockers taken daily, often for decades, by large numbers of people with

Abstract

Since the 2018 recalls of valsartan, nitrosamine impurities in sartan drug substances and tablets have been a major quality and regulatory concern. This review summarises published work on detecting these impurities by gas chromatography-mass spectrometry (GC-MS), and it reports no new data. It describes how the impurities arise in tetrazole-ring synthesis, the toxicological basis of the acceptable intake limits, sample preparation and injection options, chromatographic and mass spectral conditions, and validation. The literature shows that headspace and direct-injection GC-MS can reach the sensitivity required, though artefact formation, matrix effects and limited reporting of validation detail complicate comparison between laboratories.

hypertension. Even a small carcinogenic risk therefore matters. The episode led to a rapid expansion of testing, new regulatory guidance and a lasting change in how impurity risk is assessed throughout the pharmaceutical

industry [4, 5].

Analytical chemistry was central to the response. Laboratories had to detect compounds at parts-per-billion levels in a matrix of tablet excipients and a large excess of active substance, and the tests had to be validated and ready within weeks. Gas chromatography coupled with mass spectrometry (GC-MS) was among the first techniques used, because the small, volatile nitrosamines such as NDMA and NDEA are well suited to it, and regulators published headspace GC-MS procedures for valsartan early on [6, 7]. Liquid chromatography with mass spectrometry was used in parallel, particularly for less volatile nitrosamines. This review concentrates on the GC-MS route.

This article is a narrative review and reports no new experimental data. It draws on the regulatory documents, toxicological reports and analytical papers published up to the present, and it avoids quoting laboratory results that cannot be traced to a cited source. After a description of how nitrosamines arise in sartan synthesis and why such low limits apply, the review covers sample preparation, GC-MS conditions, method validation and the confounders that can mislead an analyst. Published findings are gathered in table 1. The last section lists the gaps that remain, including the need for harmonised reporting.

The size of the nitrosamine problem has been debated. Some authors have counted recalls across many drug classes since 2018 and noted that sartans accounted for a large share of the early cases, with ranitidine, metformin and others following [3]. The sartan cases are therefore a useful reference for understanding how analytical methods were developed under pressure, and many of the lessons about sampling, standards and verification have been carried over to later problems. Recall notices also showed how much the findings depended on the sensitivity of the tests that happened to be in use at the time.

2. ORIGIN OF NITROSAMINES IN SARTANS

N-Nitrosamines form when a secondary or tertiary amine meets a nitrosating agent, most often nitrous acid generated from nitrite under

acidic conditions [8, 9]. Nothing about this chemistry is exotic, and it has long been known from food, tobacco and water [10, 11]. What was new in 2018 was its occurrence in a pharmaceutical process. Many sartans, including valsartan, losartan, irbesartan, candesartan and olmesartan, contain a tetrazole ring that is built from a nitrile by reaction with an azide. After the reaction, residual azide is quenched with sodium nitrite in acid, creating the nitrosating agent in a vessel that may also contain amines [1, 12].

Table 1: Published GC-MS related approaches and findings for nitrosamines in sartans

Approach Context	Reported feature	Ref.
Headspace GC-MS valsartan	Combined NDMA and NDEA assay for substance and tablets using a regulatory procedure.	[7]
Headspace sampling theory	Diluent, temperature and time control partitioning of volatile analytes.	[13]
Liquid injection solvent extraction	Wider analyte range but more matrix reaches the inlet and column.	[6, 14]
Splitless injection trace analysis	Concentrates analyte on the column; liner and temperature affect discrimination.	[14, 15]
Electron ionisation SIM NDMA, NDEA	Selected ions with a qualifier ion give specificity at ppb levels.	[6, 16]
Triple quadrupole GC-MS/MS MRM	Product ion monitoring reduces chemical noise in complex matrices.	[16]
High-resolution MS metformin case	Near-isobaric interference can mimic NDMA at low resolution.	[17]
Deuterated internal standards NDMA-d6	Correct variation in partitioning, injection and response.	[6, 14]
ICH Q2 validation specificity, LOQ	Limits and accuracy shown in spiked placebo and drug substance.	[18, 19, 20]
Artefact testing spiked amine and nitrite	Heating can create nitrosamine in the vial; formation checks recommended.	[6, 21]

The amine source differed between processes. In valsartan routes the solvent N,N-dimethylformamide (DMF) can break down, or contain traces of dimethylamine, which is nitrosated to give NDMA. Where

triethylamine is used as a base, diethylamine arising as an impurity or degradation product gives NDEA [1, 12]. NMBA was linked to N-methyl-2-pyrrolidone and its degradation products [3]. Contamination was exacerbated by recovery and reuse of solvents and reagents, which carried amines and nitrosamines between batches and sometimes between products made on the same equipment [1, 22]. Regulators found that the nitrosamines were a consequence of specific process choices, not of the sartan molecule itself.

Later work widened the picture. A review of the chemistry showed that nitrosamines may arise from reagents, solvents, catalysts, packaging materials and even cross-contamination, and that trace nitrite in water or excipients can be enough in suitable conditions [9, 21]. Nitrite is a common impurity in excipients, and a published database collects measured values to support risk assessment of finished products [23]. For sartans specifically, nitrosamines were found mostly in the active substance, but formation in drug products by reaction between residual amines and nitrite excipients is possible and has to be considered. The breadth of possible routes explains why testing of every batch was not regarded as a sufficient control.

Toxicology provides the reason for concern. Small dialkyl nitrosamines such as NDMA and NDEA are potent rodent carcinogens, causing mainly liver and, in some studies, other tumours after metabolic activation by cytochrome P450 enzymes to alkylating species that damage DNA [24, 25, 26]. Dose-response work in thousands of rats established the basis for later extrapolation [25]. Not all nitrosamines are equally potent, and structure-activity analysis has shown that some are much less concerning than others [27, 28]. NDMA and NDEA belong to the potent group, so human exposure is regulated as a cohort-of-concern carcinogen with a very low acceptable level [29].

The structural logic behind the concern is well established. The N-nitroso group is a recognised structural alert for mutagenicity, and nitrosamines with an alpha-hydrogen atom on each side of the nitrogen are the ones readily hydroxylated by cytochrome P450

enzymes, giving unstable products that decompose to alkyl diazonium ions [26, 30]. These electrophiles methylate or ethylate DNA bases, and the resulting miscoding explains the potent mutagenicity. In the threshold of toxicological concern framework, nitrosamines of this kind fall in the cohort of concern, which is excluded from the generic threshold and requires compound-specific limits [29, 31]. That explains why a trace impurity attracted such stringent treatment, and why the analytical target had to be set so low.

Epidemiological evidence on exposure through contaminated valsartan is limited. A Danish nationwide cohort study found no clear increase in overall cancer risk with NDMA-contaminated valsartan, although the follow-up was short and the authors cautioned against firm conclusions about longer exposure [32]. A German analysis reported a possible association with liver cancer in people exposed to contaminated valsartan, while noting that the finding required confirmation [33]. Neither study alters the regulatory approach, which rests on the principle of keeping lifetime added risk below one in 100,000 and is deliberately precautionary. For analysts, the practical lesson is that the limits are low enough to make method sensitivity the main technical issue [18, 29].

Not every detected compound in sartans is a nitrosamine from process contamination. Some unrelated volatile impurities, such as residual solvents, co-elute or ionise in the same mass region and can generate false-positive results if identification relies on one ion only. This is one reason that confirmatory ions and retention time windows are written into most validated methods. Awareness of the process chemistry helps the analyst anticipate which nitrosamines are plausible in a given product, and so which standards should be run alongside the sample [1, 22]. A reference mixture containing every plausible nitrosamine, run at the start of method development, helps establish retention order and shows whether any pair of compounds co-elutes.

3. REGULATORY LIMITS AND SENSITIVITY

Limits follow the ICH M7 approach for DNA-reactive impurities, which defines a compound-specific acceptable intake corresponding to a negligible lifetime cancer risk [29, 31]. For NDMA and NDEA the agencies applied acceptable daily intakes of 96 ng and 26.5 ng respectively, calculated from rodent carcinogenicity data [1, 4, 5]. Other nitrosamines found in sartans were given their own limits, with NMBA at the same level as NDMA. The intake figures are fixed, and the concentration limit in a given product therefore depends on its maximum daily dose. Where several nitrosamines are present, the combined risk is assessed, with the total taken into account against the limit for the most potent compound.

A worked example shows what this demands of the analysis. For valsartan with a maximum daily dose of 320 mg, an intake of 96 ng of NDMA corresponds to a limit of 0.3 parts per million in the active substance, which is 300 ng per gram. This is a small figure, equivalent to one gram of nitrosamine dispersed through more than three tonnes of product. For NDEA at 26.5 ng, the limit is about 0.083 parts per million [1, 4]. Methods should be able to quantify well below these values. Regulators have suggested quantification limits at or below roughly 10 percent of the limit, so that results near the limit are meaningful and a modest rise in signal cannot be mistaken for noise, which for NDEA implies working at the level of 8 ng per gram or lower [4, 5]. Smaller daily doses permit higher concentration limits but do not relax the requirement for sensitivity.

Regulatory expectations extend beyond a limit test. Manufacturers were asked to carry out a risk assessment of every product, to confirm it by testing where a risk was identified, and to report changes to authorities [4, 5]. Confirmatory tests are expected to use validated, sensitive and selective methods, with the validation following the general principles of ICH Q2 as set out in practical method-validation texts [18]. The FDA published a combined headspace GC-MS procedure for NDMA and NDEA in valsartan substance and products, and European official

laboratories shared similar methods, giving the industry a common starting point [7]. These public methods were intended as references to be verified in each laboratory, not as substitutes for in-house validation.

Where the limit is applied matters for analytical planning. Sartan specifications were in practice placed on the active substance, since that is where the contamination arises, with additional control of finished tablets by risk assessment and testing as justified [4, 5]. Testing every batch was initially required for products found to contain nitrosamines, and manufacturers could later move to reduced testing once the process was shown to be free of the source, supported by a control strategy for raw materials and solvents. A laboratory methodology developed for substance may not be directly applicable to tablets, whose excipients add background and nitrite, and so each sample type needs its own demonstration of performance [1, 5].

The World Health Organization also issued advice on nitrosamine impurities, stressing quality assurance in manufacturing and cooperation between regulators [34]. Pharmacopoeial chapters on gas chromatography supply general system suitability and calibration requirements that apply to nitrosamine methods too [35]. Put simply, the documents define what a method must show: specificity for each named nitrosamine in the presence of the active substance and excipients, a quantification limit appropriate to the product's limit, linearity and accuracy over a range around that limit, and adequate precision [18, 19]. How the numbers are achieved is left to the laboratory, which explains the variety of approaches seen in the literature.

Limits have been revised and extended since 2018, and guidance for categories of nitrosamine beyond the small dialkyl compounds has appeared. Regulators now use structure-based approaches for novel nitrosamines derived from active substances, assigning acceptable intakes based on features that affect metabolic activation [27, 28]. Readers should therefore treat any numerical limit quoted in an older paper as a snapshot. Guidance documents are updated, and the

current versions should be consulted before a method is designed or its results are interpreted [4, 5]. A limit calculated from a superseded intake value may be either unnecessarily tight or insufficiently protective, and the history of revisions since 2018 illustrates how quickly positions have changed.

4. SAMPLE PREPARATION AND INJECTION

Sample preparation must dissolve or extract nitrosamines from a matrix dominated by a poorly volatile sartan. Two main approaches are used. In headspace analysis a weighed portion of powder is sealed in a vial with a high-boiling solvent such as dimethyl sulfoxide or N-methyl-2-pyrrolidone, heated, and a portion of the vapour is sampled for injection [7, 13]. Liquid injection involves extracting the substance with a solvent such as dichloromethane or methanol, sometimes with filtration or centrifugation, and injecting the clarified extract. Headspace analysis is cleaner and keeps non-volatile matrix out of the instrument, while liquid injection is more flexible and extends to less volatile analytes [6, 13]. In either case the sample weight is a trade-off: more powder lowers the detection limit in the original material but also loads the system with more sartan.

The headspace conditions deserve care. Equilibration temperature and time determine how much analyte reaches the gas phase, and the partition coefficient depends strongly on the diluent [13]. Higher oven temperatures raise sensitivity but risk artefact formation, as residual amines and nitrite in the sample may react to produce nitrosamines during heating. Many published procedures therefore use moderate temperatures, in the region of 100 to 140 °C, and some add reagents to inhibit nitrosation, such as ascorbic acid or a sulfamic acid solution, though this changes the matrix [6, 21]. Vial headspace volume and sample mass also affect the response, and each should be fixed in the method.

Extraction recovery is a validation item in its own right. Spiked recovery from the real sample matrix is determined at several levels, normally from the quantification limit up to about 150 percent of the limit, with

acceptance criteria in the region of 80 to 120 percent for trace analysis [18, 19]. Poor recovery can come from loss of volatile analyte during weighing and transfer, adsorption to glass or filters, or incomplete extraction from poorly soluble powder. Shaking is preferred over sonication, which warms the sample and can promote artefacts, and centrifugation is usually chosen over filtration to avoid contact with membranes. Standard and sample solutions should be analysed within a stated time, since stability in the chosen diluent is not guaranteed [13, 20].

Isotopically labelled internal standards, typically NDMA-d6 and NDEA-d10, are standard practice. They behave almost identically to the target through extraction, partitioning and injection, and they correct for variations in headspace equilibrium, injection volume and detector response [6, 14]. Calibration solutions are prepared in the same diluent, preferably also with blank or placebo matrix, since matrix can change recovery. Because nitrosamines are volatile, standards should be prepared in sealed containers and stored cold, and light should be avoided, as nitrosamines undergo photolysis. Solvents of the highest purity are essential, since NDMA is a ubiquitous trace contaminant in many laboratory reagents [8, 11].

Liquid injection raises its own issues. Dichloromethane extracts the nitrosamines efficiently but can also extract much of the sartan, which then contaminates the inlet liner and the first part of the column. Splitless injection concentrates analyte on the column for sensitivity, but requires an inlet liner and temperature chosen to avoid discrimination and thermal degradation [14, 15]. Large-volume or programmed-temperature vaporiser injection can improve detection limits further. The inlet is also where artefacts may form, and a hot, active surface can convert co-injected amines and nitrite residues to nitrosamines, so a clean deactivated liner and routine maintenance are important parts of the method rather than minor details [6, 14].

Direct comparison between headspace and liquid injection shows trade-offs and not a clear winner. Headspace methods are simple

to automate and rugged, and they reach the required limits for the volatile nitrosamines NDMA and NDEA, but they are less suitable for NMBA and other polar, less volatile compounds [6, 7]. Liquid injection can cover a wider range but needs more cleanup and instrument maintenance. Laboratories routinely choose according to the nitrosamines of concern for the product, the instrument available and the throughput required. Method transfer between laboratories is helped by publishing fixed parameters such as diluent, temperature, time, split ratio and liner type.

Sample homogeneity and sampling plan are rarely discussed but affect the reliability of results. Contamination in a batch of drug substance may not be uniformly distributed, particularly if it comes from a solvent residue or a contaminated reactor surface, so a result from a single small sample might not represent the batch. Taking multiple independent samples, and testing each at least in duplicate, reduces this risk. Retained samples from earlier batches can be useful to establish when a contamination began. For finished tablets, grinding a number of units to a homogeneous powder is the usual approach, though grinding generates heat and should be done gently with cooling [6, 7].

5. GC-MS SEPARATION AND DETECTION

Column choice follows the polarity of the analytes. Polar polyethylene glycol (wax) phases, mid-polarity cyanopropylphenyl phases such as the 624 type, and low-polarity 5 percent phenyl phases have all been used for volatile nitrosamines [6, 14]. Wax columns give strong retention and good peak shape for NDMA and NDEA and separate them from the solvent front, but they are temperature-limited and sensitive to water and oxygen. Typical columns are 30 m in length with an internal diameter of 0.25 mm and a film of about 1 μm , with helium carrier gas at constant flow. Oven programmes start near 40 to 60 °C to retain NDMA, then ramp to elute the other nitrosamines.

Instrument parameters beyond the column also influence performance. Inlet temperature is a compromise between rapid vaporisation

of the sample and minimising thermal reactions, and published procedures often use values from about 200 to 250 °C [14, 16]. The transfer line and ion source are held hot enough to prevent condensation of the matrix, but not so hot as to cause excessive fragmentation of the small molecular ion. A solvent delay protects the filament from the solvent peak, and a short run is feasible because the target nitrosamines elute early. Carrier gas flow, split ratio and oven ramp are normally fixed in the validated method and checked in robustness experiments in which each is varied slightly [18, 19].

Detection is by electron ionisation at 70 eV, which produces reproducible fragmentation and library-searchable spectra [14, 16]. NDMA has a molecular mass of 74 and gives an abundant molecular ion, with fragments at m/z 42 and 43 used for confirmation. NDEA, with mass 102, shows a molecular ion and characteristic fragments, among them m/z 44, 56 and 57 [6, 16]. Single quadrupole instruments operate in selected ion monitoring mode, recording only chosen ions for greatly increased sensitivity compared with full scan. Quantification uses the most abundant specific ion, while at least one qualifier ion, with a defined ratio to it, protects against false positives.

Tandem mass spectrometry improves selectivity further. In a triple quadrupole instrument operating in multiple reaction monitoring mode, a precursor ion is selected, fragmented, and one or more product ions monitored, which removes most chemical noise from complex matrices [16]. GC-MS/MS has been widely adopted for sartans because its selectivity allows lower limits and cleaner baselines, especially for liquid injection with larger sample loads. High-resolution accurate-mass instruments have also been used, mainly with liquid chromatography, and have shown that near-isobaric interferences can produce false NDMA signals, as in a report on metformin that showed how mass resolution decides whether a peak is truly NDMA [17]. The lesson transfers to GC-MS: low mass resolution leaves room for interference.

Published approaches are summarised in table 1, with the categories of entry shown in

fig. 1. The table shows a consistent set of choices: headspace or liquid sample introduction, deuterated internal standards, selected ion monitoring or multiple reaction monitoring, and validation against ICH criteria [6, 7, 18]. Where numerical performance is reported, limits of quantification for NDMA and NDEA are typically in the low ng per gram range, adequate for the sartan limits, though values vary by method and instrument. The entries also show that most information on sartans is found in regulatory methods and analytical reviews, not in many independent primary papers, which limits the strength of cross-method comparison [1, 3, 6].

Carryover and system contamination deserve attention at these levels. Sartans are heavy, poorly volatile compounds that accumulate in the inlet, and later injections can show ghost peaks or shifting response. Frequent liner changes, blank injections between samples and periodic column trimming are standard precautions, and some laboratories use backflushing to expel high-boiling material after each run [13, 14]. Septum bleed and contaminated vials can also give signals at the NDMA mass. A reagent blank, a placebo blank and a system blank run at the start of each sequence enable the analyst to discriminate between a real contaminant and an instrumental source.

Instrument sensitivity is not the only determinant of detection limits. Signal-to-noise depends on the baseline, which is set by column bleed, carrier gas purity and detector condition, and on the injected quantity, which is limited by how much of the matrix the system tolerates. Practical limits therefore differ from instrument specifications, and the quantification limit has to be demonstrated in the real matrix for a stated sample concentration. A method claiming a limit at a sample concentration that cannot be dissolved or sampled in practice is of little use, and reports should state sample amount, solvent volume and injection volume [19, 20].

Round-robin or inter-laboratory comparison would be the most direct way to establish how well GC-MS methods agree. Official laboratories in Europe and North America

have shared methods and in some cases compared results during the sartan crisis, but few of these exercises have been published in full [1, 7]. Proficiency schemes for nitrosamines in drug substances are only beginning to appear. Wider publication of such data would help manufacturers choose and verify methods with more confidence, and would show how large the real analytical uncertainty is at the low ng per gram level.

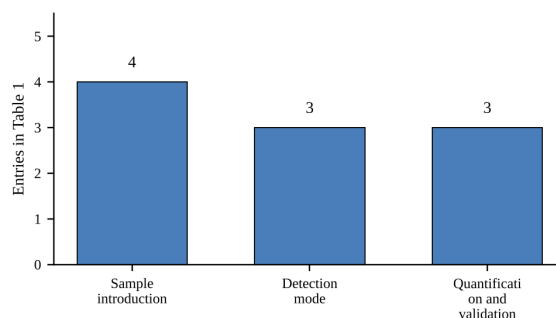


Fig. 1: Number of entries in table 1 by analytical stage

6. VALIDATION, CONFOUNDERS AND GAPS

Validation follows ICH Q2 and covers specificity, linearity, accuracy, precision, detection and quantification limits, and robustness [18, 19]. Specificity is shown by injecting blank, placebo, individual nitrosamine standards and spiked samples, and confirming absence of interference at the retention times. Linearity usually spans from the quantification limit to about 150 percent of the specification, with recoveries of 80 to 120 percent expected at trace level. Detection and quantification limits may be estimated from signal-to-noise ratios of about 3 and 10, or from the standard deviation of low-level responses and the calibration slope, and the second approach is statistically more defensible [19, 20]. Verification of the limit with spiked samples at that level is a final check.

Matrix effects require specific assessment. In GC-MS they differ from the ion suppression seen in electrospray, but active sites in the inlet and column can be masked by matrix components, increasing the response of a given analyte compared with a clean standard [14, 36]. Comparing calibration slopes in solvent and in matrix, or measuring recovery in spiked samples, reveals the extent of such

effects. Deuterated internal standards correct many of them. Different sartans, and different batches or manufacturers of one sartan, have different excipients and impurity profiles, so a method validated for one product cannot be assumed to work for another without verification [6, 7].

System suitability and routine quality control keep a validated method valid in use. Each analytical sequence typically begins with blank injections to confirm the absence of carryover and then a standard at or near the quantification limit, which must meet a minimum signal-to-noise ratio, followed by replicate injections of a standard to check repeatability of the response ratio [18, 20]. Retention times and qualifier ion ratios are compared with acceptance windows, and a check standard is injected at intervals and at the end to demonstrate that the response has not drifted. Control charts of internal standard areas can indicate a failing septum, liner or filament before data quality is lost, and pharmacopoeial chromatography chapters provide the general frame for these checks [35].

The main confounder is artefactual formation of nitrosamines during analysis. If a sample contains secondary amines and nitrite, heating in a headspace oven or a hot injector may generate nitrosamine that was never in the product, giving a falsely high result. Methods have therefore been designed to test for the problem, for example by spiking amine and nitrite into a nitrosamine-free matrix and checking for formation, or by comparing results at different temperatures [6, 21]. The same concern led regulators to caution about GC-based methods for other products, and for such cases an orthogonal liquid chromatographic method is a sensible confirmation [17]. Artefact testing should be a routine part of validation for any GC-MS method.

Several gaps remain in the literature. Few independent studies compare GC-MS procedures head to head on the same sartan samples, so differences in reported sensitivity may reflect laboratory skill or instrument as much as method design [3, 6]. Reporting is uneven: many papers omit the sample amount, diluent, liner, split ratio or ion ratios

needed to reproduce a procedure. Collaborative studies between laboratories would help to define reproducibility. Long-term monitoring data from market surveillance would also be valuable. Finally, methods for the wider range of possible nitrosamines, including less volatile and drug-substance-related compounds, are developing, and GC-MS will need to be set against newer techniques in that context [9, 22, 28].

7. CONCLUSION

Gas chromatography-mass spectrometry has proved a workable and sensitive way to detect the small volatile nitrosamines found in sartans. The published regulatory procedures and reviews show that headspace or liquid sample introduction, deuterated internal standards and selected ion or tandem mass spectrometric detection can quantify NDMA and NDEA well below the limits that follow from the acceptable daily intake [1, 4, 6, 7]. These limits are low because of the carcinogenic potency of the compounds and the long duration of sartan therapy [24, 25, 29]. The same analytical principles carry across to newer nitrosamine problems.

The method must still be handled with care. Artefact formation, matrix effects and carryover can all mislead, and the literature gives too little detail for easy comparison between laboratories [6, 14, 21]. Collaborative studies, fuller reporting of method parameters and orthogonal confirmation by liquid chromatography are the most useful improvements. For routine control, analysts should pair validated GC-MS methods with process-based risk assessment, since testing alone cannot guarantee the absence of contamination [4, 5]. Collaboration between regulators, manufacturers and academic laboratories will continue to be needed, and published methods should carry enough detail that others can reproduce them without guesswork. Only then can the evidence base become as dependable as the limits it is meant to support.

8. ABBREVIATIONS

DMF-N,N-Dimethylformamide, EI-Electron ionisation, GC-MS-Gas chromatography-mass

spectrometry, GC-MS/MS-Gas chromatography-tandem mass spectrometry, ICH-International Council for Harmonisation, LOQ-Limit of quantification, MRM-Multiple reaction monitoring, NDEA-N-Nitrosodiethylamine, NDMA-N-Nitrosodimethylamine, NMBA-N-Nitroso-N-methyl-4-aminobutyric acid, SIM-Selected ion monitoring

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10. AUTHORS CONTRIBUTIONS

All the authors have contributed equally.

11. CONFLICT OF INTERESTS

Declared none

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