# Research on Nitrosamines in Cosmetics: A Review

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**Abstract**

As a kind of toxic and strongly carcinogenic substance, nitrosamines are likely to be present in the raw materials of cosmetics, or during the preparation, storage, and transportation processes. This would result in the potential hazard to the health of consumers. This paper carries out the study on nitrosamines. Firstly, the physical and chemical properties of nitrosamines as well as their types in cosmetics are introduced. Then, the formation reasons and possible reaction mechanisms of nitrosamines in cosmetics are summarized. Next, various detection methods of nitrosamines are concluded and compared. The legislation, norms, and standards for nitrosamines in cosmetics around the world are listed. Finally, the development trends of detection, supervision, and management for nitrosoamines in cosmetics are predicted.

**Keywords:** Nitrosamines; Cosmetics; Toxic substances; Nitrosamine detection; Cosmetic hazards

## Introduction

Economic development and the pursuit of beauty make the cosmetics market vigorous, and cosmetics are essential for the peoples in their daily life. Due to the strong purchasing power, China has become the second largest market of cosmetics in the world. It has been reported by National Bureau of Statistics that the total retail sales of cosmetics of China in 2021 reached 402.6 billion yuan, increasing by 18.41% in comparison with 340 billion yuan in 2020. Hence, the average annual rate is higher than that of other countries. Moreover, the number of licensed cosmetics manufacturers is 5,400, and the number of products with legal licenses reaches up to 1.6 million. Hence, the cosmetics have a wider develop space in China [1]. As is well known, cosmetics are a kind of mixture produced according to scientific formulations. During the processes of production, processing, storage and transportation, some harmful substances could be generated or brought into, thus posing a threat to the consumers' health. Among them, nitrosamines are the common hazards with obvious carcinogenicity, as well as easily produced by the reaction between precursor secondary amine and nitrite. Simultaneously, the reaction can progress well under the natural conditions or in the human and animal bodies. They can enter our bodies via the respiratory tract, digestive tract, or skin. Moreover, not only can the long-term low dose cause cancer, but also a shock of higher dose can directly result in carcinogenesis [2]. Therefore, the nitrosamines harm has undoubtedly been paid close attention to. Moreover, it is of great research significance and application value to know the sources, influence factors, formation mechanisms and detection methods of nitrosamines in cosmetics to effectively inhibit the formation of nitrosamines.

## Nitrosamines Profile

The nitrosamines have significant carcinogenicity, which is related to their chemical structures, physical and chemical properties, tissues and organs, metabolic process, etc. However, until now, the specific mechanism has still not been clear. The existing findings suggest that the increase of electron-withdrawing ability of hydrogen at $\alpha$-C ($R^1$ and $R^2$) attached to ammonia nitrogen decreases the electron cloud and density of $\alpha$-C and N-nitroso-group and increases the number of static charges. This would make the hydrogens on the carbon atom more reactive, and easily oxidized, decomposed, isomerized to alkyldiazohydroxides *in vivo*. As a highly active carcinogen, this compound can block

DNA replication and induce gene mutation [3]. Furthermore, some researchers have found that the carcinogenicity of nitrosamines might be related to the free radical activity. For example, Hirata et al. have shown that the N-nitrosamine compounds in the tobacco could induce the generation of reactive oxygen species, stimulate the Wnt signal path, and thus resulting in the lung cancer.

All the countries issue the standards for the contents of nitrosamines in cosmetics. However, there are still many cosmetics with a lower content of nitrosamines, and then they can't be analyzed and detected at the present stage. Furthermore, due to the complex raw materials and limited detection means, the generation condition and formation mechanism are still unknown, which further increases the difficulty to effectively inhibit the content of nitrosamines in cosmetics. In this paper, the types of nitrosamines, generation causes, reaction mechanisms, detection means, regulations and standards in various countries

are summarized, so as to provide the references for relevant manufacturers, consumers, supervisors, and researchers.

## Types and Sources of Nitrosamines

## Types of nitrosamines

There are many types of nitrosamines in cosmetics (Figure 1), of which the most common one is N-Nitrosodiethanolamine (NDELA). In 1997, the Food and Drug Administration (FDA) first reported that the detection rate of NDELA in cosmetics was up to 31% with the content of 1~130000 μg/kg [4,5]. In 1986, 2-isoctyl-4-(N-nitroso-N-methylamino) benzoic acid (NMPABAO) was detected in the sunscreens, as well as a familiar type of nitrosamine. Notably, with more attention to the cancer risk of nitrosamines and the progress of detection technology, more than 300 types of nitrosamines have been detected in cosmetics. The frequently detected ones are listed in Table 1.

**Table 1:** Frequently detected nitrosamines in cosmetics and their sources.

| Types | Abbreviation | Formula | Possible sources | References |
|---|---|---|---|---|
| N-nitrosodiethanolamine | NDELA | $C_4H_{10}N_2O_3$ | shower gel, shampoo, hand sanitizer | [6] |
| 2-ethylhexyl 4-(N-methyl-N-nitrosamino) benzoate | NMPABAO | $C_{16}H_{24}N_2O_3$ | Sunscreen, hair dye | [7] |
| N-nitroso dimethylamine | NDMA | $C_2H_6N_2O$ | Sunscreen, shampoo, perfume | [8] |
| N-nitrosodiethylamine | NDEA | $C_4H_{10}N_2O$ | Shampoo, shaving foam, body lotion | [9] |
| N-nitrosodipropylamine | NDPA | $C_6H_{14}N_2O$ | Face cream, toner | [10, 11] |
| N-nitrosodibutylamine | NDBA | $C_8H_{18}N_2O$ | Sunscreen, hair conditioner, vanishing cream | [12] |
| N- nitrosomorpholine | NMOR | $C_4H_8N_2O_2$ | Shower gel, mascara, shampoo | [13] |
| N-nitrosodiphenylamine | NDPHA | $C_{12}H_{10}N_2O$ | Shampoo, facial cleanser, hair dye | [14] |
| N-nitrosopseudolepine | NAB | $C_{10}H_{13}N_3O$ | Skin whitening products, after sun lotion | [15] |
| N-nitrosopiperidine | NPIP | $C_5H_{10}N_2O$ | Water aqua, Shampoo, loose powder | [16] |
| N- nitrosopyrrolidine | NPYR | $C_4H_8N_2O$ | Vanishing cream, gel products | [17] |
| N-nitrosodibenzylamine | NPBZA | $C_{14}H_{14}N_2O$ | Cosmetic boxes, bottles, bags | [18] |
| N-nitroso-N-methylaniline | NMPHA | $C_7H_8N_2O$ | Shampoo, facial cleanser, facial mask | [19] |
| N-nitroso-N-ethylaniline | NEPHA | $C_8H_{10}N_2O$ | Cosmetics package, Rubber dropper head for | [20] |
| N-nitrosodiisopropanolamine | NDPLA | $C_6H_{14}N_2O_3$ | Facial cleanser, shampoo, shower gel | [21] |
| N-nitroso-methyloctadecylamine | NMODA | $C_{19}H_{40}N_2O$ | Hair softener | [22] |
| N-nitroso-methyldodecylamine | NMDDA | $C_{13}H_{28}N_2O$ | Lipstick, eye cream | [23, 24] |
| N-nitroso-dicyclohexylamine | NDCHA | $C_{12}H_{22}N_2O$ | Facial mask, facial cleanser | [18] |
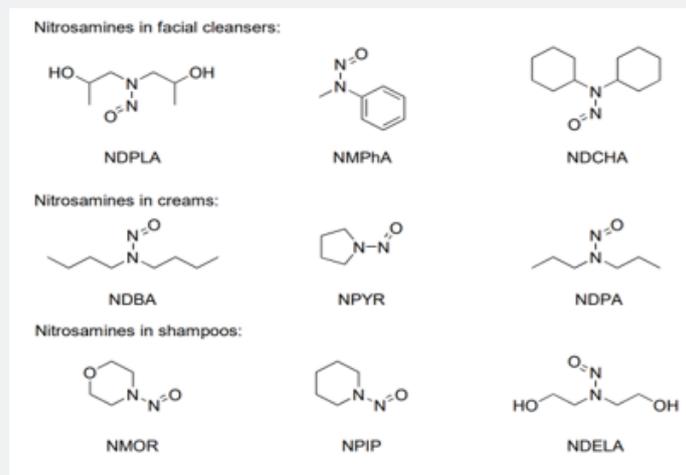
**Figure 1:** Typical nitrosamines in cosmetics

## Sources of Nitrosamines

**Raw materials:** Since nitrosamines were detected in cosmetics in 1977 for the first time, most researchers regard the raw materials as an import source of the nitrosamines. From 1980 to 1984, FDA detected 1 mg/kg of nitrosamines in about 30% cosmetics [25]. Joo et al. [26] detected NDELA in multiple raw materials of cosmetics (triethanolamine, trimethylamine, coconut fatty acid diethanolamide, fatty acid chain alkanolamide, and triethanolamine-dodecyl sulfate) with high-performance Liquid Chromatography-tandem Mass Spectrometry (HPLC-MS-MS) method. Guo Huifang [27] analyzed the several typical nitrogen-containing surfactants in cosmetics, such as coconolic acid monoethanolamide (CMEA), cocoanut fatty acid n, n-diethanolamide (CDEA), and castor oil acylthreonine sodium, simultaneously, established an efficient and simple method to detect the NDELA in nitrogen-containing surfactants.

In 2014, the detection limit and quantification limit of volatile nitrosamines in ten types of cosmetics were determined in China [28]. However, the complex raw materials of cosmetics could result in the increase of the types of hazards introducing the nitrosamines. Cocoamidopropyl betaine (CAB) is common in cosmetics, and widely used in washing products such as shower gel, shampoo, and hand sanitizer. It has a quaternary ammonium group with strong electronic induction, which makes the carboxylic acid group attached to the quaternary nitrogen atom always present in a salt-like group, and thus showing amphoteric ions characteristics. Hence, CAB is a kind of better surfactant [29]. The synthesis of CAB includes three steps, that is, synthesis of cocamidopropyl dimethylamine, neutralization between chloroacetic acid aqueous solution and alkali, and synthesis of coir amide propyl betaine, as shown in Figure 2.
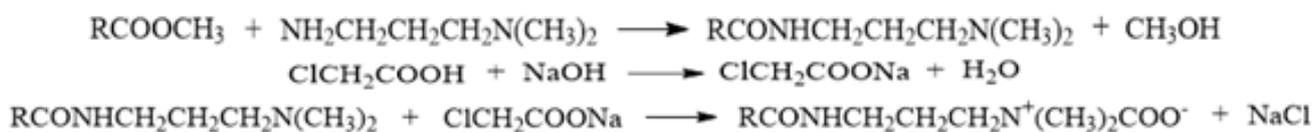


**Figure 2:** Synthesis of CAB.

Both the raw materials for synthetizing CAB and intermediate products have the tertiary amine structure. Moreover, once the tertiary amine structure contacts with the nitrosation reagents such as nitrite and nitrate, the nitrification reaction would occur. Therefore, there would possibly form a tiny amount of nitrosamines during the synthesis process of CAB, resulting in the potential risk of nitrosamines in the products.

**Preparation process:** In addition to the raw materials, the preparation process of cosmetics is also an important source of nitrosamines. Under the effect of nitrosification reagents, the precursors (primary amine, secondary amine, and tertiary amine) can form nitrosamine compounds. Among them, the secondary amine is more prone to nitrosation reaction [30]. At present, there are many nitrosation reagents, i.e., $HNO_2$, $NO$, $NO_2$, $N_2O_3$, $N_2O_4$, NOX

(X=Cl and Br), various nitrates, and nitrites. If the cosmetics contain diethanol amine (DEA), triethanolamine (TEA), nitrosation agent, and fatty acid alkanolamide as the emulsifier or pH modifier, there would form nitrosoamines under certain conditions [31]. As such, the formation mechanism relates with pH. Under acidic conditions, $HNO_2$ can directly react with amines, or two $HNO_2$ molecules can react with each other to form $N_2O_3$ and $H_2O$. Then, $N_2O_3$ forms nitrosamine after one-step reaction. For example, the nitrosation reaction of N, N-dimethylaniline can progress under the acidic condition, and this reaction can be divided into two steps (Figure 3). Firstly, the nitrous acid forms the nitrosyl cation in an acidic environment. Subsequently, the nitrosyl cation attacks the nitrogen atoms as the electrophile, thus forming the nitroso cation intermediate of nitrogen. Then, according to the different classifications of amine, the substituents attached to nitrogen atom with positive charge of intermediate are different. When the hydrogen atoms are attached to nitrogen atoms of primary amine and secondary amine, they can be directly removed to form nitrosamine. On the contrary, there are no hydrogen atoms attached to the nitrogen atoms, so failing in dehydrogenation. However, the dimethylamino is an active group, and the nitroso cation can form C-Nitroso compound through the electrophilic substitution on the para-position of the benzene ring [31].
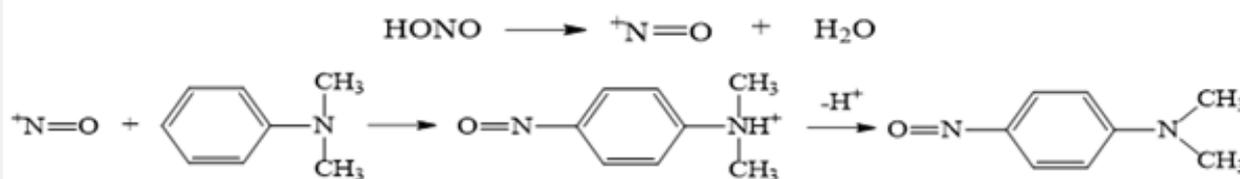


**Figure 3:** Nitrosation of N, N-dimethylaniline.

Nitrosamines are relatively stable under non-acidic conditions, whereas the resonant structure resulting from conjugated effect between lone pair electrons and nitroso could make the H attached to α-C easily oxidized. Moreover, as the electron withdrawing group is attached to α-C, the electron cloud densities of α-C and N-NO would be decreased. Simultaneously, the H attached to α-C would be more active and easily be oxidized. In 2002, CHOI et al. [32] have reported that NDMA could be formed in the waste water with chloramine, and simultaneously, they proposed the reaction mechanism (Figure 4). Notably, DMA can react with $NO^{2-}$ to form NDMA under the catalysis effect of formaldehyde, trichloroacetaldehyde, and carbonyl compound such as acetaldehyde, acetone and trifluoroacetaldehyde [33]. Bromonitropropanol is the common preservative and fungicide in cosmetics with the content of 0.04%~0.1%. When pH is 8~12, $Br^-$, $NO^{2-}$ and formaldehyde could be released from bromonitropropanol after decomposition, and then catalyzes their reactions with DMA to form NDMA (Figure 5). Hence, our law requires that the content of bromonitropropanol should not exceed 0.1%.
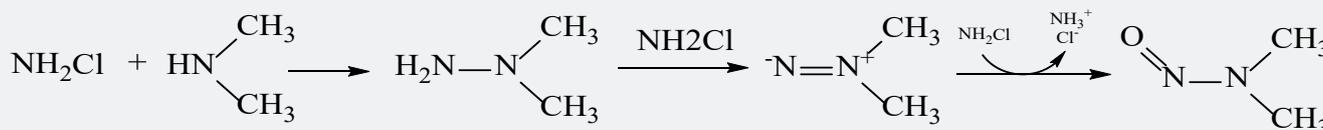


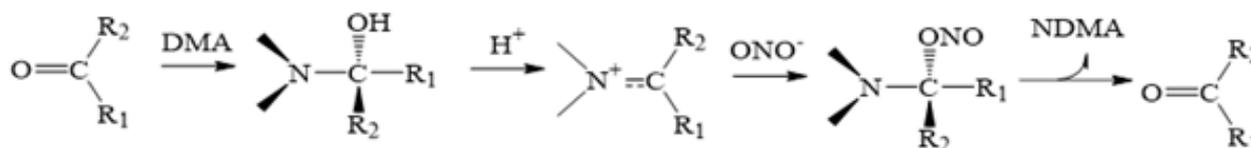**Figure 4:** Formation of NDMA by reaction between chloramine and methyleneamine.



**Figure 5:** Formation of NDMA by nitration of carbonyl compounds.

**Storage process:** Generally, the preservatives and stabilizers are added to cosmetics for the long-term storage and good performance. The surfactant, viscosifier, pH regulator, emulsifier and antibacterial preservative with secondary amine can all catalyze the potential nitrosation reaction at temperatures above 35°C or at acidic pH [34]. In addition, the storage vat with the nitrite for anti-corrosion and some packaging materials with residual toxic solvent might result in the nitrosamines formation. The packaging materials of cosmetics are mainly based on plastic, and simultaneously, N, N-DMA is widely applied in the packaging materials due to high thermal stability, low corrosion, and low toxicity. Thus, the DMA in the plastic containers could volatilize and shift to the contents, resulting in polluting the cosmetics [35].

## Detection Methods of Nistrosamines

It is greatly difficult to detect the nitrosoamines in cosmetics, attributed to more types, lower content, greater difference in the properties of nitrosamines, and possible false positive disturbance of new nitrosamine formed in the analysis process [36]. At present, the frequently-used detection methods include gas chromatography (GC), liquid chromatography (LC), gas chromatography-mass spectrography (GC-MS), UV-VIS spectrophotometry, thin layer chromatography, micellar electrokinetic capillary chromatography (MECC), polarography, surface-enhanced Raman scattering method (SERS), etc. Furthermore, for the detection of volatile nitrosamines in water substrate, nitrogen phosphorous detection (NPD) and nitrogen chemiluminescence detection (NCD) methods are used as the mass spectra (MS) for cost reduction.

GC is a chromatographic separation and analysis method using gas as mobile phase, suitable for qualitative and quantitative analysis for volatile organic compounds. In principle, the gas sample is brought to the chromatographic column by carrier gas. The forces between stationary phase and sample components in column are different, so the components can be separated from each other due to their different outflow time from column. Similarly, the LC takes liquid as the mobile phase, and the components in mixture are separated in dependence on the difference in the affinity of each component for two phases. This method is characterized by high efficiency, high sensitivity, and simple operation.

As can be seen by comparison, the GC-MS has not only the separation capability of GC but also the highly sensitive identification capability of MS. GC-MS/MS is used to detect 14 nitrosamines in 44 types of drugs such as sartan and ranitidine. Compared with HPLC, LC-MS has a higher column efficiency and separation speed, withstands higher column pressure and faster flow rate. Thus, LC-MS has the higher peak capacity and separation effect. Small volatile nitrosamines such as NPMA has been detected in active pharmaceutical ingredient (API) by Vogel et al. [37] using LC-MS/MS (Figure 6). (b) Ion chromatograms of all the nitrosamines detected after adding 50 ng/ml aqueous reference solution. (c) Ion chromatograms of quantitative nitrosamines extracted with their own LOD value.



**Figure 6:** Workflows of aqueous extraction and organic extraction steps of NDMA in API, respectively

The thermal analysis technology (TEA) is usually used with GC or LC together. The nitrosamines mixture is firstly separated, and then the N-NO bond breaks after through the TEA cracking chamber. The released nitroso (NO) is oxidized by ozone to electronically excited $NO_2$. Accordingly, the decayed radiation intensity is in proportion to the concentration of NO [38]. Because of some advantages such as high sensitivity, high precision and rapid detection, so this method has been widely applied in many fields. The methods mentioned above can qualitatively and quantitatively detect the unknown samples, but they still have some disadvantages of tedious preprocessing process, high detection cost, long detection period, expensive instruments, etc.

In recent years, Luo et al. used Raman spectra detection based on the surface enhanced Raman scattering (SERS) of precious metals to detect the trace nitrite ions in aqueous solution of nitrosation (Figure 7). This technology can make the signal intensity increase by $10^8 \sim 10^{12}$ times, and effectively improve the sensitivity of traditional Raman detection in trace analysis. Moreover, it has advantages such as ease of operation, strong selectivity, freedom from interference of water molecules, and fingerprint spectrum, so with a better detection effect for illegal additives in cosmetics, i.e., nitrosoamines, Rhodamine B, hydroquinone, and crystal violet. Representative detection methods of nitrosamine are listed in Table 2.

**Table 2:** Common of nitrosamines as well as their advantages and disadvantages.

| Detection methods | Advantages and disadvantages | Substance | References |
|---|---|---|---|
| GC | 1. High efficiency, high sensitivity, and strong selectivity, suitable for volatile substances. <br> 2. Vulnerable to pollution for detector, complex pretreatment operation (especially for non-volatile substances), comparison and correction with given data as qualitative and quantitative analysis. | NDEA <br> NDPA <br> NDBA | [42] |
| GC-NPD | 1. Especially sensitive to the volatile organic compounds with nitrogen and phosphorus, and mainly for the detection of trace nitrogen and phosphorus compounds. <br> 2. Limited application scope and higher operating cost of equipment's. | NNN <br> NAT <br> NAB <br> NNK | [43] |
| GC-MS | 1. High detection speed, sensitivity, and precision <br> 2. Good selectivity, qualitative ability, and anti-interference ability <br> 3. Small application scope, high detection cost for one-time, different pretreatment methods for different cosmetic samples, and tedious operation. | NDMA <br> NPIP <br> NDBA <br> NMEA | [44] |
| HPLC | 1. High selectivity and resolution. <br> 2. Wide application range, without limitation for the sample volatility. <br> 3. Low reliability, need of suitable mobile phase and desolvent, complicated operation, and high cost. | NDMA <br> NDEA <br> NDPA <br> NDBA | [45] |
| LC-MS | 1. High column efficiency, fast separation, and better separation effect. <br> 2. High accuracy and sensitivity, need of less samples. <br> 3. Expensive instrument and high maintenance cost. | NAB <br> NAT <br> NNN | [46] |
| GC/LC-TEA | 1. Simpleness and high efficiency, suitable for large-scale detection, high sensitivity (the pg level of detection limit), and wide linear range. <br> 2. Expensive instrument, high specificity, difficult for large-scale application. <br> 3. Higher risk of false positive results, small application range, and poor universality. | NMPLE <br> NMPABAO | [47] |
| UV-VIS | 1. Simple operation, and direct measurement of nitrosamine content. <br> 2. High interference, low detection accuracy and precision. | NDMA <br> NMEA <br> NDPA <br> NMOR | [48] |
| TLC | 1. Simple operation, fast response, short spread time, and better separation ability than paper chromatography. <br> 2. Worse repeatability and reproducibility of Rf value, and difficult to preserve chromatography. | NMPHA <br> NMBA | [49] |
| MEKC | 1. High column efficiency, high selectivity, and fast analysis speed. <br> 2. Less sample consumption, high automation degree, and suitable for the analysis and processing of samples with complex components. <br> 3. High cost, and complicated operation. | NDMA <br> NMEA <br> NDEA <br> NPYR | [50] |
| DPP | 1. High sensitivity, good resolution, good reproducibility, less sample consumption. <br> 2. Easy block of capillary, high purity of samples, and low anti-interference ability. | Nitrite nitrogen | [51] |
| SERS | 1. High sensitivity, and wide application for trace sample. <br> 2. High sensitivity and specificity, without interference from others, easy operation, and with fingerprint spectrum. <br> 3. Influence of different precious metals bases on SERS performance. | Nitrite ion | [52] |

**Table 3:** Norms and standards related to nitrosamines in cosmetics.

| Specification/standard document of nitro-samines | Standard Number | Country/Organization | References |
|---|---|---|---|
| Hygienic Standard for Cosmetics | SPGG 20201207001-2020 | Ministry of Health of the People's Republic of China | [53] |
| Determination of 10 volatile nitrosamines such as NDMA in cosmetics by GC-MS/MS | GB/T 29669-2013 | General Administration of Quality Supervision, Inspection and Quarantine of the People 's Republic of China | [23] |
| | | Standardization Administration of China | |
| Safety and Technical Standards for Cosmetics | SPGG 20201207002-2020 | Food and Drug Administration of the People's Republic of China | [54] |
| Detection and Determination of NDELA in Cosmetics by HPLC, Post-column photolysis and Derivatization. | ISO 10130-2009 | International Organization for Standardization | [55] |
| Cosmetics - Analysis methods - Nitrosamines: Technical Guidance Document for Reduction and Determination of N-nitrosamines in Cosmetics | ISO/TR 14735:2013 | International Organization for Standardization | [56] |
| Cosmetics - Analysis Methods - Nitrosamines: Detection and determination of NDELA in Cosmetics with HPLC-MS-MS | BS ISO 15819-2014 | British Standards Institution | [57] |
| | | | |
| Cosmetics - Analysis Methods - Nitrosamines: Detection and determination of NDELA in Cosmetics with HPLC-MS-MS | NF T75-631-2008 | Association Francaise de Nor-malisation | [58] |
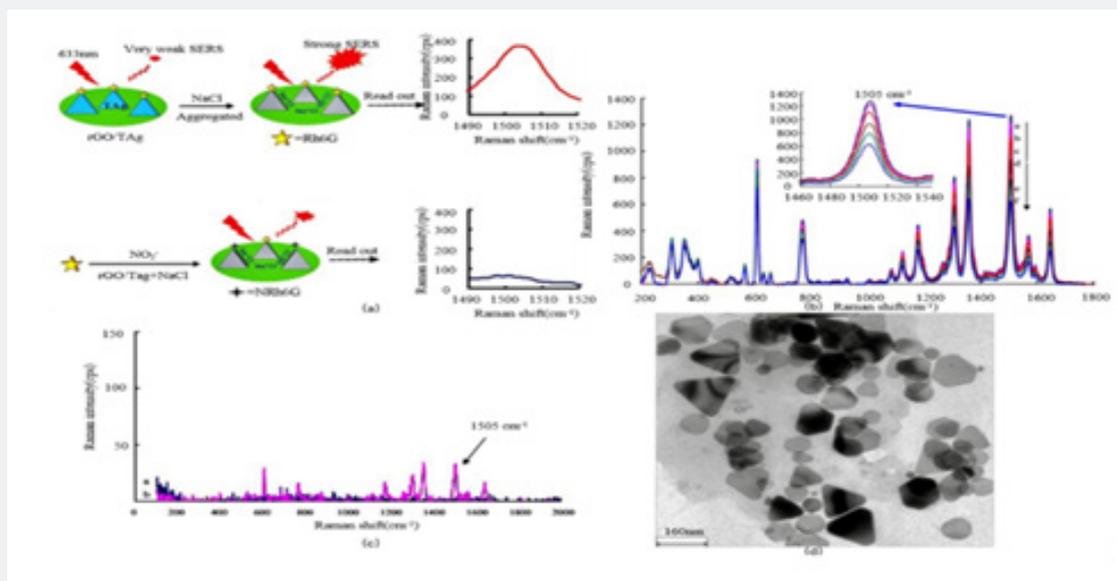


**Figure 7:** (a) The principle of rGO/TAgA/Rh6G SERS nanosensor to detect NO2−; (b) SERS spectra of the Rh6G-KBr-nitrite-rGO/TAg-NaCl system, (c) SERS spectra of NRh6G; (d) TEM image of the TAg-aggregates.

Furthermore, there has been a difficulty in directly analyzing the target due to more types of cosmetics and complex components. It is necessary to select an appropriate pretreatment method according to the target to be quantified. The target should be detected after the enrichment of purified samples. At present, the pretreatment technologies of common cosmetic samples include the digestion method, liquid-liquid extraction method, solid phase extraction method, microextraction techonology, microwave-assisted extraction method, ultrasonic-assisted extraction method, etc. [41] added cerium dioxide into porous silicon dioxide (SBA-15). The nitrosoamines are extracted from cosmetic samples with solid-phase microextraction, and meanwhile, the stirring rod is used to improve the adsorption efficiency. This solid-phase microextraction-GC-MS method is very sensitive and efficient in the detection of trace nitrosamines in cosmetics with the stirring rod support base on Ce-SBA-15 development. Miralles et al. [17] detected seven kinds of trace prohibited N-nitrosoamines in cosmetics using reversed phase dispersion-liquid-phase microextraction-LC. Accordingly, the results show that the enrichment factor is up to 65, detection limit is 1.8⊠50 ng/g, with a better repeatability (RSD < 9.8%). More importantly, this method is used to detect different samples of cosmetics, and then obtaining the equal relative recovery (80~113%).

## Norms and Standards related to Nitrosoamines in Cosmetics

The GB/T 29669-2013 published in 2014 stipulates the detection methods, detection limits and quantitative limits of ten types of nitrosamines such as NDMA in cosmetics. The industry development, technology progress and cosmetics supervision demand prompt the State Food and Drug Administration to revise the Cosmetic Safety Code, and then the cosmetic safety technical specification (2015) was put forward. A total of 944 kinds of nitrosamines are listed in the prohibited substances table, such as N-nitroso dimethylamine, N-nitroso dipropylamine, and N-Nitrosodiethanolamine. In addition, the standards of the nitrosamines contents in cosmetics are introduced at abroad. For example, the International Organization for Standardization has issued the detection and analysis method for NDELA in cosmetics and proposed the Technical Guide Document. British Standards Institution has published the standard detection method of NDELA in cosmetics. Likewise, France has issued the standard determination method of NDELA in cosmetics. Table 3 lists the norms and standards related to nitrosamines in cosmetics.

## Conclusion

With constant improvement of cosmetics performance, their components are more and more complex. Because of long-term contact with skin, the strongly carcinogenic substance in cosmetics such as nitrosoamines could result in greatly potential hazard to the human body. Although some nitrosamine compounds are prohibited in cosmetics in national standards, their coverage and completeness can't meet the safety supervision demand of cosmetics. Moreover, the nitrosamines detection could be interfered by matrix components of cosmetics, and the existing detection means are insufficient. Therefore, more effort should be devoted to establishing rapid, large-scale, sensitive, accurate and low-cost detection methods for nitrosamines, as well as improving relevant standards and specifications in future. Simultaneously, much attention to the cosmetics' safety and intensification of industrial supervision would make the studies on nitrosamines contamination in cosmetics develop toward the norms of cosmetics.

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