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Analytical Chemistry of New Psychoactive Substances: Methods, Applications and Future Prospects

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Abstract

New psychoactive substances (NPS) are a class of artificially designed and synthesized chemical substances designed to mimic the pharmacological effects of traditional drugs. They are characterized by significant structural diversity and rapid iteration and have become a major public health challenge threatening global public health. This article systematically reviews the taxonomic characteristics, epidemiological status, and research progress of major testing and detection methodologies for NPS. Based on the classification framework established by the United Nations Office on Drugs and Crime (UNODC) and the European Union Drugs Agency (EUDA) this article systematically describes the chemical structure, pharmacological properties, and modes of abuse of representative NPS such as synthetic cathinones, synthetic cannabinoids, phenethylamines, synthetic opioids, and benzodiazepines; as well as the working principles, application scope, analytical efficacy, and methodological advantages and disadvantages of chromatography-mass spectrometry, spectroscopic techniques, immunoassay techniques, and novel rapid detection techniques. Addressing the key bottlenecks currently facing the NPS detection field, such as prominent structural diversity, complex metabolic pathways, and a lack of standards, this article further proposes future development directions for detection technologies, including the widespread application of high-resolution mass spectrometry, the construction of artificial intelligence-assisted compound identification systems, the promotion of microfluidic chip technology, and the integration of green analytical chemistry principles.

Keywords

New Psychoactive Substances, Testing and Detection, Chromatography-Mass Spectrometry, Rapid Screening, Forensic Toxicology

1. Overview of New Psychoactive Substances

1.1. Definition and Classification

NPS are a class of artificially designed and synthesized chemical substances intended to mimic the psychoactive effects of traditional drugs such as cannabis, cocaine, and 3,4-methylenedioxymethamphetamine. They are often referred to as "designer drugs", "laboratory drugs", or third-generation drugs. These substances are produced by subtly modifying the chemical structures of known controlled drugs to circumvent existing laws, and therefore often circulate illegally under the guise of "legal stimulants" during periods of regulatory vacuum. According to the World Health Organization (WHO), NPS specifically refers to "pure chemical substances or products containing such substances that are not listed in the United Nations Single Convention on Narcotic Drugs (1961) and the Convention on Psychotropic Substances (1971) but may pose a potential or actual threat to public health".

Table 1. Main categories and representative substances of new psychoactive substances.

Category	Representative substances	Chemical family	Main pharmacological effects	Common forms
Synthetic cannabinoids	JWH-018 5F-MDMB-PICA	Aminoalkylindoles, indazole carboxamides	Cannabis-like effects (euphoria, relaxation), can induce anxiety, psychotic symptoms	Herbal mixtures, e-cigarette liquids, powders
Synthetic cathinones	Methcathinone *α*-PVP MDPHP	Cathinone derivatives	Excitement, euphoria, increased social desire; sympathomimetic effects	White/Brown powder, crystals, tablets
Phenethylamines	2C series NBOMe series	Phenethylamine derivatives	Hallucinogenic, altered perception; sympathomimetic effects	Paper, tablets, powders
Synthetic opioids	Fentanyl analogues MT-45	Fentanyl derivatives, piperazines	Analgesia, sedation, euphoria; severe cases can cause respiratory depression	Powder, tablets, patches
Benzodiazepines	Flunitrazepam etizolam	Benzodiazepine derivatives	Sedation, hypnosis, anti-anxiety, anterograde amnesia	Tablets, powders, solutions

The classification system of NPS is diverse and continues to evolve with the emergence of new substances. As shown in Table 1, which briefly lists the main categories of new psychoactive substances and representative substances. Currently, the internationally accepted classification methods are mainly based on two core dimensions: chemical structure and pharmacological effects. The European Monitoring Centre for Drugs and Drug Addiction (EMCDDA) classifies them into eight categories, specifically including synthetic cannabinoids, synthetic cathinones, phenethylamines, synthetic opioids, benzodiazepines, piperazines, tryptamines, and other unclassified substances. The United Nations Office on Drugs and Crime (UNODC) has a more refined classification; as of 2024, its early warning system had included 1259 NPSs, classifying them into 14 categories for global NPS monitoring. From a pharmacological effect perspective, NPS can be divided into four main categories: stimulants (such as synthetic cathinones), hallucinogens (such as phenethylamine derivatives), sedatives (such as synthetic opioids), and cannabinoid receptor agonists (such as synthetic cannabinoids). It should be noted that there is some overlap and intersection between these categories [1].

1.2. Epidemiology and Hazards

NPS pose a significantly greater threat to public health than traditional drugs, with their core threats primarily manifested in the following dimensions: First, their toxicity characteristics are highly unpredictable. Limited by the lack of systematic and standardized toxicological research data, the safe dose thresholds for most NPS have not been clearly defined, and the toxicity differences among different derivatives within the same structural family are extremely significant. Taking synthetic cannabinoids as a typical example, potent derivatives such as 5F-MDMB-PINACA can have pharmacological activity levels 100 - 300 times higher than natural tetrahydrocannabinol (THC), and exposure to extremely low doses can induce severe poisoning reactions, even endangering life. Second, their pharmacological effects exhibit complex multi-target characteristics. Most NPS, while acting on their primary pharmacological targets, can also non-specifically interfere with the normal function of other neurotransmitter systems. For example, synthetic cathinones can not only significantly inhibit the reuptake of dopamine and norepinephrine but may also disrupt the homeostasis of the serotonergic system, thereby inducing fatal and serious adverse events such as serotonin syndrome.

Acute poisoning incidents caused by NPS abuse have been rising rapidly in recent years. Their clinical manifestations are diverse, severe, and complex, primarily manifesting as severe cardiovascular toxicity (including hypertension, tachycardia, and arrhythmias), neuropsychiatric abnormalities (including anxiety attacks, psychotic symptoms, and status epilepticus), and metabolic disorders (including high fever and rhabdomyolysis). In severe cases, it can progress to multiple organ failure, ultimately leading to death. Furthermore, long-term NPS abuse is closely associated with irreversible cognitive impairment, the development of chronic mental disorders, and organic organ damage, and its high potential for dependence further exacerbates the long-term harm to public health.

2. Representative New Psychoactive Substances and Characteristics

2.1. Synthetic Cathinones

Synthetic cathinones are a class of artificially synthesized stimulants with structural similarities to natural cathinones (excitatory alkaloids found in khat). They are often disguised as "bath salts" or "plant fertilizers" to evade relevant regulations. As the second largest category of NPS, more than 130 synthetic cathinones have been identified globally as of 2024. According to the "Trends in High-Risk Drug Use and NPS" report jointly released by (EMCDDA) and Europol in 2017, 14 new substances in this class were discovered for the first time in 2017 alone. The "World Drug Report" released by the United Nations Office on Drugs and Crime (UNODC) in 2018 specifies that approximately 12 - 14 new synthetic cathinones were reported globally for the first time in 2017. According to the 2017 World Drug Report by the United Nations Office on Drugs and Crime (UNODC), of the 739 NPS reported worldwide since 2009, 19% belong to the synthetic cathinone class, totaling as many as 140 [2]. The chemical core of these substances is the *β*-ketophenylethylamine structure. By modifying the benzene ring, amino group, and alkyl side chains, hundreds of structural variants can be derived. Representative substances include methcathinone (4-MMC), methylenedioxymethcathinone, *α*-pyrrolylpentanone (*α*-PVP), and 3,4-methylenedioxy-*α*-pyrrolylhexanoylphenylone (MDPHP). The chemical structure of a representative synthetic cathinone is reflected in **Figure 1**.

The main routes of abuse for synthetic cathinones include nasal inhalation, oral administration, and injection. After oral administration, a significant pharmacological effect can appear within 15 - 45 minutes; nasal inhalation provides rapid onset within minutes, with a duration of pharmacological action typically lasting 2 - 4 hours. These substances belong to the monoamine transporter inhibitor class and can effectively block the reuptake of dopamine, norepinephrine, and serotonin, leading to a significant increase in the concentration of monoamine neurotransmitters in the synaptic cleft. The efficacy of a drug is closely related to its chemical structure: pyrrole-substituted derivatives (such as *α*-PVP and MDPV) have higher selectivity for dopaminergic and norepinephrine systems, thus their excitatory effects are more significant and their potential for dependence is also higher; while methylenedioxy-substituted derivatives (such as methylenedioxymethcathinone) exhibit stronger serotonergic activity and their hallucinogenic effects are more prominent.

Synthetic cathinone compounds have strong psychogenic effects and are considered to have similar stimulating effects on the human body as cocaine, methamphetamine, MDMA, etc. While providing users with a pleasurable sensation, they can also cause significant side effects on the central nervous system, cardiovascular system, and respiratory system, including sweating, tachycardia, hypertension, anxiety, paranoia, etc. [3] Compared to traditional stimulants such as cocaine, synthetic cathinones significantly increase the risk of inducing psychotic symptoms, and during withdrawal, they can manifest as severe depression, extreme fatigue, and intense drug cravings, further exacerbating the harm caused by their abuse.

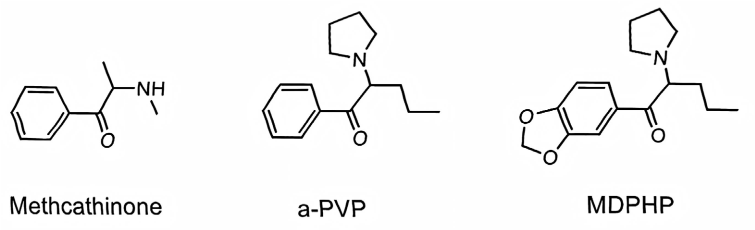

Figure 1. Chemical structure of representative synthetic cathinones.

2.2. Synthetic Cannabinoids

Synthetic cannabinoids are not single compounds, but a class of artificially synthesized cannabinoid receptor agonists with highly diverse structures and continuous evolution. As the largest and most structurally diverse category of NPS, more than 330 synthetic cannabinoids have been reported to the United Nations Office on Drugs and Crime (UNODC) early warning system since 2013. These substances are artificially designed and synthesized, belonging to the category of complete cannabinoid receptor agonists, and can specifically interact with the body's own endogenous cannabinoid system. Patel *et al.* reported that synthetic cannabinoid receptor agonists (SCRAs) possess significantly greater potency and efficacy at the CB_1 receptor than natural Δ^9-THC. The most potent SCRA, 4CN-CUMYL-BUTINACA, exhibited an EC_{50} of 0.11 nM, which is far lower than the EC_{50} of 28.18 nM for THC, indicating strong inhibition of cAMP production [4]. The chemical structures of synthetic cannabinoids are highly diverse, and based on their core structure, they can be divided into several subcategories, including classical cannabinoids, non-classical cannabinoids, hybrid cannabinoids, and aminoalkyl indoles. The emergence of "semi-synthetic" cannabinoids in recent years, obtained by structurally modifying natural cannabinoids, further increases the structural complexity and regulatory difficulty of this class of substances. **Figure 2** shows the general formula for the synthesis of cannabinoids.

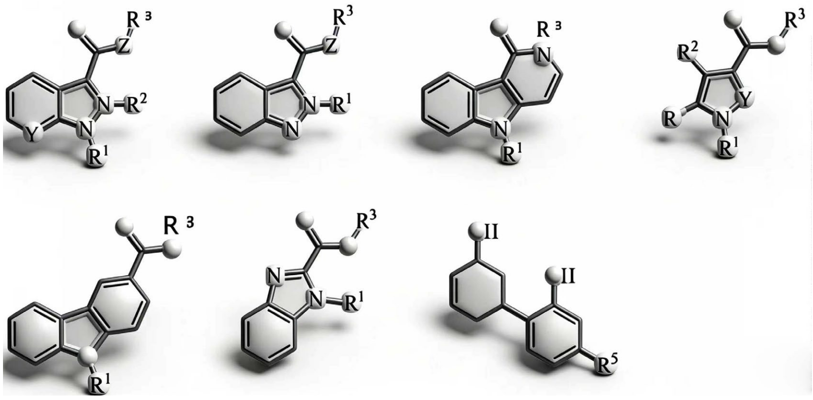

Figure 2. General formula of synthetic cannabinoids.

Traditionally, synthetic cannabinoids have been illegally circulated primarily through spraying on herbal mixtures, often disguised as "Spice" or "K2" to evade regulation. Their abuse is mainly through smoking in rolled cigarettes or hookah. In recent years, their circulation has diversified, with e-liquids, powders, tablets, and capsules becoming increasingly common, further increasing the concealment of abuse and the difficulty of regulation. Synthetic cannabinoids are artificially synthesized agonists of endocannabinoid CB1 and CB2 receptors, which combine cannabinoids with receptors and produce stronger physiological and pharmacological effects than natural cannabinoids. For example, the effect of HU-210 synthesized by Raphael Mechoulam is 100 - 800 times stronger than that of THC [5]. Compared to natural cannabis, synthetic cannabinoids lack components such as cannabidiol (CBD) with anxiolytic and antipsychotic activities, making their abuse more likely to induce serious adverse events.

The harm of synthetic cannabinoid abuse has a clear dual nature: short-term abuse effects mainly include tachycardia, hypertension, anxiety attacks, psychotic symptoms, epileptic seizures, and acute kidney injury [6]. Long-term abuse can lead to cognitive impairment, severe drug dependence, and specific withdrawal syndrome. Of particular concern is the frequent association of synthetic cannabinoid abuse with outbreaks of mass poisoning, often triggered by the same batch of illicit products, resulting in multiple users simultaneously experiencing severe poisoning symptoms. This phenomenon suggests serious deficiencies in dosage control and quality control during the illicit manufacturing process. From a testing perspective, the extensive metabolic characteristics of synthetic cannabinoids (a single parent compound can produce dozens of metabolites) and their low blood concentrations (often in the ng/mL or even pg/mL range) constitute the main technical challenges for their analysis and detection.

2.3. Other Major Categories

Phenylethylamine-type NPS are a class of synthetic compounds characterized by potent hallucinogenic effects. They mainly include the 2C series (such as 2C-B and 2C-I) and the NBOMe series (such as 25I-NBOMe and 25B-NBOMe). These substances are often illegally circulated in the form of “paper sheets,” *i.e.*, blotting paper soaked in the drug. Their main mode of abuse is sublingual or oral mucosal absorption. Among them, NBOMe compounds exhibit particularly significant pharmacological activity. Their effective pharmacological dose is only 50 - 200 μg, less than one-tenth of the effective dose of lysergic acid diacetamide (LSD), but the risk of acute overdose is extremely high, having caused numerous cases of acute poisoning and death worldwide. From the perspective of mechanism of action, this type of substance, as a potent agonist of 5-hydroxytryptamine 2A (5-HT2A) receptor, can induce strong hallucinogenic effects such as visual distortion, synesthetic experience and altered self-awareness. It may also induce serious adverse events that endanger life, such as severe hypertension, epileptic seizures, and high fever. The chemical structures of the representative 2C and NBOMe series are shown in **Figure 3**.

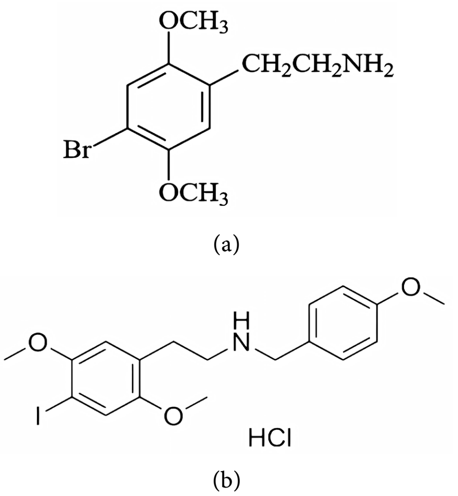

Figure 3. (a) Chemical structure of 4-bromo-2,5-dimethoxyphenethylamine; (b) Chemical structural formulas of representative 2C series and NBOMe series.

Synthetic NPS are mainly represented by fentanyl analogues (such as carfentanil and acetylfentanil) and non-fentanyl derivatives (such as MT-45 and U-47700). As shown in **Figure 4**, MT-45, a piperazine-based synthetic opioid, was initially developed as a candidate analgesic in the 1970s and is currently mainly circulated in the illicit market in the form of its dihydrochloride salt. The core danger of this class of substances lies in their extremely high pharmacological potency and narrow therapeutic window. Carfentanil, for example, has a pharmacological potency up to 10,000 times that of morphine; even minute overdose can induce respiratory depression and lead to death. Compared to traditional opioids, some synthetic opioids (such as MT-45) can also induce unique adverse reactions, specifically skin pigmentation, hair loss, and ocular toxicity, further expanding their scope of harm to human health.

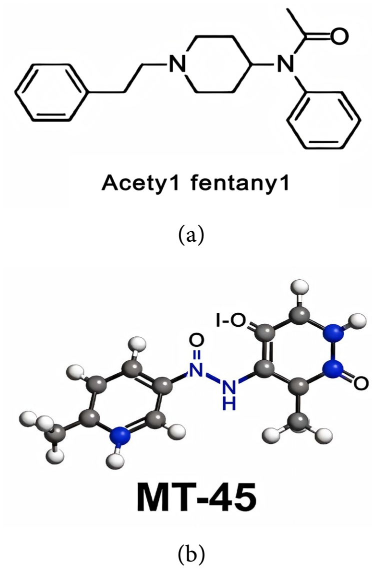

Figure 4. Chemical structural formulas of acetylfentanyl and MT-45.

NPS in the benzodiazepine class, typically represented by flunitrazepam, etizolam, and flualprazolam (The structure is shown in **Figure 5**), have chemical structures similar to traditional benzodiazepines, and their sedative, anxiolytic, and anterograde amnesic effects are significantly stronger than those of traditional drugs. These substances are frequently used illegally in drug-induced sexual assault cases, primarily because they are difficult to detect in routine drug screenings and possess physicochemical properties such as being soluble in alcohol, colorless, and odorless, making them highly concealed. In recent years, the abuse of benzodiazepine NPS has shown a prevalent trend of mixed abuse, with its use in combination with other NPS classes (especially synthetic cathinones) becoming increasingly common. The primary purpose of abuse is to alleviate the overstimulation effects of stimulants. However, this mixed abuse pattern significantly increases the complexity of multidrug interactions, further raising the health risks and safety hazards associated with abuse.

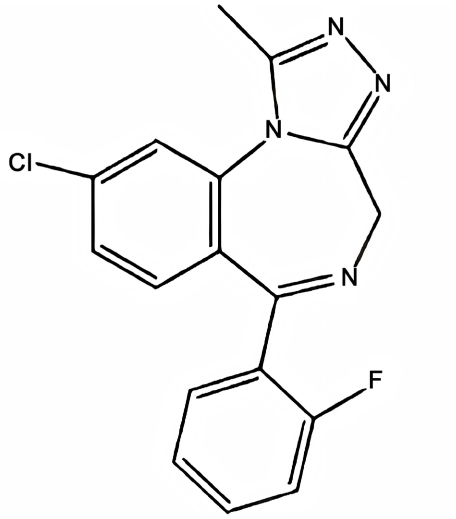

Figure 5. Chemical structure of flualprazolam.

3. Advances in New Psychoactive Substance Testing and Detection Methodologies

3.1. Chromatography-Mass Spectrometry

Liquid chromatography-tandem mass spectrometry (LC-MS/MS) is currently the gold standard technology for the detection of NPS, especially suitable for the qualitative and quantitative analysis of trace NPS and their metabolites in biological samples. This technology integrates the high separation efficiency of liquid chromatography with the high sensitivity and specificity of mass spectrometry, enabling the simultaneous detection of various structurally heterogeneous NPS. Currently, Ultra-high performance liquid chromatography-tandem mass spectrometry (UHPLC-MS/MS) has undergone systematic optimization based on traditional LC-MS/MS technology. By adopting chromatographic column packing material with smaller particle size (<2 μm) and higher operating pressure (>1000 bar), the analytical rate and separation efficiency are significantly improved. Currently, a simple and sensitive LC-MS/MS method is used to simultaneously detect six novel synthetic opioids (carfentanil, fentanyl, etc.) and two hallucinogens (psilocybin, lysergic acid) and their main metabolites in whole blood. The method uses protein precipitation pretreatment, optimizes precipitation solvent volume, formic acid concentration, and centrifugation time, and achieves high linearity ($R^2 > 0.99$) in the range of 0.1 - 20 ng/mL, with a detection limit as low as 0.05 ng/mL (except for lysergic acid, which is 1 ng/mL), and is suitable for analysis of both live and post-mortem samples. The experiment verified the accuracy, precision (%RSD < 13%) and resistance to matrix interference of the method. Only 50 μL of sample is required, which significantly improves the detection efficiency of forensic laboratories and the level of green chemistry practice [7]. Quadrupole time-of-flight mass spectrometry (UHPLC-QTOF MS/MS) is an ultra-high performance liquid chromatography method that can simultaneously detect four cathinone-based new psychoactive substances in blood samples: 3,4-methylenedioxymethcathinone (Methylone), 3,4-methylenedioxyethylcathinone (Ethylone), 4-chloromethcathinone (4-CMC), and 4-chloroethylcathinone (4-CEC) [8]. Ultra-high performance liquid chromatography-tandem quadrupole time-of-flight mass spectrometry can even screen 150 drugs and toxins in human whole blood [9]. Relevant research reports have shown that a rapid detection method based on simple protein precipitation pretreatment combined with ultra-high performance liquid chromatography-tandem mass spectrometry (UHPLC-MS/MS) has been established, which can realize 22 synthetic opioids and synthetic cannabinoids in whole blood samples. Simultaneous quantitative analysis of substances and their metabolites. The chromatographic run time of this method is only 7.5 minutes, and the detection limit is as low as 0.05 ng/mL [10].

Gas chromatography-mass spectrometry (GC-MS) technology has certain limitations in NPS detection due to the need for sample derivatization to enhance volatility. However, it still has unique application value for some volatile or semi-volatile NPS (such as some synthetic cathinones and piperazines). The core advantage of GC-MS technology lies in its mature spectral library search system, which allows for preliminary qualitative identification of unknown compounds through comparison with standard spectral libraries such as NIST. However, the application scope of GC-MS technology is significantly limited for thermally unstable or highly polar macromolecular NPS (such as most synthetic cannabinoid glucuronide conjugates).

The core methodological challenges of chromatography-mass spectrometry (GC-MS) lie in three main aspects: First, the supply of reference standards is scarce, with many novel NPS lacking commercially available standards; second, matrix effects are complex, especially in biological samples where ion suppression or enhancement effects are prone to occur, affecting detection accuracy; and third, the identification of metabolites is difficult, as the *in vivo* metabolic pathways of most NPS are not yet fully elucidated. To address these methodological bottlenecks, researchers have developed high-resolution mass spectrometry (HRMS) coupled with liquid chromatography, such as LC-QTOF-MS (quadrupole-time-of-flight mass spectrometry) and LC-Orbitrap-MS. These techniques can achieve efficient screening of unknown and unexpected NPS through precise mass number determination and isotope distribution analysis, without the need for pre-prepared standards [11].

3.2. Spectroscopic Detection Technology

Raman spectroscopy and Fourier transform infrared spectroscopy (FTIR), as non-destructive and rapid screening techniques, are playing an increasingly important role in the on-site detection and initial screening of NPS. These techniques, based on the characteristic spectra generated by molecular vibrational energy level transitions, can provide unique "fingerprint" spectral information of compounds, enabling preliminary identification of target substances. Portable Raman spectrometers are widely used in rapid NPS screening at customs, public security, and other law enforcement sites, and can complete the preliminary qualitative identification of suspicious powders, tablets, and plant materials within seconds.

Surface-enhanced Raman spectroscopy (SERS), by adsorbing the target sample onto a nanoscale rough metal surface, can enhance the Raman signal by up to 10^6 times, significantly improving detection sensitivity, with its detection limit reaching the single-molecule level [12]. This technology has unique advantages in trace NPS detection and target analyte detection in complex matrices. For example, it can effectively detect trace targets such as flunitrazepam added to beverages and synthetic cathinone metabolites in urine. Related studies have shown that the combination of SERS technology and chemometric methods is gradually developing into a powerful technical tool for rapid on-site NPS screening.

While nuclear magnetic resonance (NMR) spectroscopy is not used for routine NPS screening, it has irreplaceable core value in NPS structure confirmation and identification of unknown compounds. Among them, two-dimensional NMR techniques (such as COSY, HSQC, and HMBC) can provide complete molecular structure characteristics, covering key parameters such as atomic connection modes and stereochemical configurations, and are a key technical means for forensic laboratories to perform structural analysis on novel NPS.

The limitations of spectroscopic techniques in NPS detection are mainly reflected in relatively low sensitivity (especially for trace NPS in biological samples), significant matrix interference (other coexisting components in complex samples can easily mask the characteristic signal of the target analyte), and weak resolution of isomers (structurally similar NPS derivatives tend to produce similar characteristic spectra). Based on these limitations, spectroscopic techniques are usually used as a primary screening method for NPS, and positive screening results need to be further confirmed by chromatography-mass spectrometry.

3.3. Immunoassay Technology

Immunoassay, based on the specific binding reaction of antigen and antibody, has advantages such as simple operation, no need for complex instruments, fast analysis rate, high throughput detection, and controllable cost. It has significant application value in large-scale primary screening and rapid point-of-care testing of NPS. Enzyme-linked immunosorbent assay (ELISA) and fluorescence polarization immunoassay (FPIAs) are currently the two most widely used immunoassay techniques in clinical testing and field screening. Specific detection kits have been successfully developed for major NPS categories such as synthetic cannabinoids, synthetic cathinones, phenethylamines, and synthetic opioids, effectively meeting the technical needs of routine NPS initial screening.

However, the application of traditional immunoassays in NPS detection still faces many severe technical challenges: First, the high structural diversity of NPS leads to unpredictable antibody cross-reactivity, affecting detection specificity; second, the development of specific antibodies for emerging NPS is lagging, resulting in a shortage of specific antibodies; third, existing antibodies are mostly designed to target NPS parent compounds, exhibiting weak recognition ability for their metabolites, thus increasing the difficulty of metabolite detection. To address the aforementioned technical bottlenecks, researchers are dedicated to developing novel immunoassay platforms. These platforms, centered on a mixture of broad-spectrum specific antibodies and polyclonal antibodies, can specifically identify common structural epitopes of a particular class of NPS, thereby significantly improving the detection efficiency for novel NPS structural analogs.

Lateral flow immunochromatographic assay (LFIA) strips, as a rapid diagnostic technology, are increasingly used in on-site NPS screening. Modern LFIA strips employ a multi-detection-line design, enabling simultaneous screening of multiple NPS categories. Some commercially available LFIA products can simultaneously detect 10 or more common NPS. The detection limits of these strips are typically in the ng/mL range, effectively covering the therapeutic and toxic concentrations of most NPS, meeting the core needs of rapid on-site screening. It is important to note that LFIA results are mostly semi-quantitative or qualitative. Positive samples obtained from screening require further confirmatory testing using chromatography-mass spectrometry (GC-MS) to ensure the accuracy and reliability of the results, providing a scientific basis for subsequent research and law enforcement.

3.4. Novel Rapid Detection Technology

With the rapid development of micro-nano technology and sensor technology, a series of novel rapid detection platforms have been gradually developed and applied to the field of real-time on-site monitoring of NPS. Electrochemical sensors, based on the principle of electrochemical analysis, achieve qualitative and quantitative detection of target analytes by accurately detecting changes in current signals generated by the redox reaction of NPS on the electrode surface. This technology possesses significant advantages such as high detection sensitivity, fast response rate, and simple and portable equipment structure. In recent years, electrochemical sensors based on functionalized nanomaterials (such as graphene, carbon nanotubes, and metal-organic frameworks) have shown significantly improved overall detection performance. The detection sensitivity of some sensors can reach a level comparable to liquid chromatography-tandem mass spectrometry (LC-MS/MS), effectively expanding their application scope in the field of NPS detection.

Molecularly imprinted polymers (MIPs) technology precisely prepares polymer materials with specific recognition holes for target NPS, simulating the specific recognition function of "artificial antibodies." Compared to natural antibodies, MIPs exhibit superior environmental stability (withstanding high temperatures, extreme pH environments, and various organic solvents), lower preparation costs, and longer shelf life, making them particularly suitable for NPS detection scenarios under extreme environmental conditions. Coupled with sensor technologies (such as MIP-modified quartz crystal microbalance (QCM) sensors), highly selective detection of specific NPSs can be effectively achieved, further improving the specificity and accuracy of the detection process [13].

Table 2. Comparison table of new psychoactive substance detection technologies.

Technology category	Represent active methods	analysis speed	Sensitivity	Specificity	Main application scenarios	Limitations
Chromatography-mass spectrometry	LC-MS/MS, UHPLC-MS/MS	Moderate (5 - 30 minutes/sample)	Extremely high (pg/mL level)	Extremely high	Forensic quantitative analysis, clinical toxicology confirmation, metabolic studies	Expensive instruments, requires professional operation, complex pre-treatment
Spectroscopic technology	Raman spectroscopy, FTIR	Rapid (<1 minute/sample)	Low to medium (%)	High to medium	Rapid on-site screening, initial screening, identification of seized drugs	Low sensitivity, strong matrix interference, difficult to distinguish isomers
Immunoassay	ELISA, FPIAs	Rapid (5 - 20 minutes/sample)	High (ng/mL level)	Low to medium	Large-scale screening, point-of-care testing, initial screening	Multiple cross reactions, easy missed detection of new substances, semi quantitative analysis
New type of sensor	Electrochemical sensors, molecular imprinting	Extremely fast (seconds)	High	Medium	Real-time monitoring, portable devices, high-throughput screening	Insufficient stability, limited multiplex detection capability

Microfluidic chip technology integrates core operational units such as sample pretreatment, separation, and detection onto a micrometer-scale chip carrier, realizing the core design concept of a "lab-on-a-chip". This technology has outstanding technical characteristics such as extremely low sample requirements (only microliters (μL)), low reagent consumption, and fast analysis rates. It is particularly suitable for rapid on-site NPS screening and detection in resource-constrained environments, effectively meeting the needs for high efficiency and convenience in on-site testing. As shown in Table 2, a comparison of technologies for detecting new psychoactive substances was made.

4. Analysis of Detection Strategies and Application Scenarios

4.1. Selection and Characteristics of Biological Matrices

The selection of biological matrix for the detection of NPS directly determines the accuracy of the detection results and the scientific interpretation of the results. Different biological matrices have their own unique physicochemical properties and detection advantages, suitable for different detection application scenarios, as follows:

Blood (including whole blood, plasma, and serum) is the optimal biological matrix for assessing acute NPS poisoning and recent exposure, accurately reflecting the current drug concentration and pharmacological effect intensity in the body. Blood NPS concentrations are well correlated with clinical poisoning manifestations, but this matrix has limitations such as a short detection window (usually several hours to several days) and invasive sampling procedures. Related studies have shown that some NPSs exhibit significant post-mortem redistribution in blood. For example, 3,4-methylenedioxy-α-pyrrolidinyl hexanoyl phenyl ketone (MDPHP) showed no significant difference in concentration between central and peripheral blood 3 - 4 hours post-mortem (1639.99 ng/mL vs. 1601.90 ng/mL, respectively), while vitreous fluid showed a difference in concentration between the two eyes, suggesting that the eyeball is not a homogeneous matrix for post-mortem redistribution [14].

Urine, as a non-invasive sampling matrix, has the advantages of a long detection window (usually 2 - 5 days, depending on the drug's half-life) and rich metabolite information, making it suitable for large-scale NPS screening and abuse monitoring. Most NPS are excreted in urine primarily as metabolites; for example, synthetic cannabinoids are mainly excreted as glucuronic acid conjugates of their hydroxylated and carboxylated metabolites. A liquid chromatography-tandem mass spectrometry (LC-MS/MS) detection method has been established, which can simultaneously detect multiple synthetic cathinones and their related metabolites in urine, with a detection limit of 0.1 - 0.5 ng/mL, covering most clinically relevant concentration ranges [15].

Hair provides long-term exposure history information for NPS (Non-Physical Drug Sensing), typically reflecting drug use over several weeks to months, and has significant value in forensic identification, used to assess drug use patterns, timing of use, and chronic abuse. However, hair analysis faces numerous technical challenges, including external contamination, differences in pigment binding, and the lack of threshold standards to distinguish between incidental and chronic drug use. The concentration of synthetic cathinones in hair ranges from low pg/mg to ng/mg, and this concentration variation is closely related to drug dosage, frequency of use, and hair type.

Saliva is increasingly used as a minimally invasive sampling matrix. This matrix reflects the concentration of free drugs in the blood and is suitable for recent use assessment of NPS and roadside drug screening. The window period for saliva testing is typically several hours to one day, comparable to that of blood testing, but the sampling process is simpler and easier. For some NPS (such as synthetic cathinones), the concentration ratio in saliva to blood is relatively stable, making saliva concentration a reliable surrogate indicator of blood concentration, thus providing technical support for non-invasive testing.

Cerebrospinal fluid (CSF), as a biological matrix in direct contact with the central nervous system, has unique application value in forensic pathology research. Because it is less affected by postmortem redistribution effects, drug concentrations in CSF more accurately reflect the pre-death brain drug concentrations in research subjects. A 2024 study validated an LC-MS/MS detection method that can quantitatively detect 39 abused drugs (including multiple NPS) in CSF, providing a new research perspective for the toxicological interpretation of fatal NPS poisoning cases [16].

4.2. Clinical Applications and Forensic Scenarios

In emergency medicine settings, the detection of NPS relies on rapid, accurate, and reliable testing technologies to provide reliable scientific support for clinical diagnosis and treatment decisions. For patients suspected of NPS poisoning, rapid immunoassay screening techniques (such as urine drug screening) can provide initial diagnostic direction, but their limitations must be fully considered: most NPS do not show significant cross-reactivity during routine immunoassays, easily leading to false negative results. Therefore, clinicians should not rely solely on toxicology screening results but must combine them with the patient's specific clinical manifestations (such as tachycardia, hypertension, psychotic symptoms, etc.) for a comprehensive assessment. The rapid development of bedside mass spectrometry (such as portable gas chromatography-mass spectrometry (GC-MS) instruments) is gradually changing this situation, enabling emergency departments to obtain accurate confirmatory test results in a short time, providing strong support for clinical diagnosis and treatment.

Forensic medical examinations place more stringent technical requirements on NPS testing, demanding highly accurate results credible in court. In this context, the industry typically employs a three-tiered testing strategy: initial screening using immunoassay, confirmatory testing using GC-MS or liquid chromatography-tandem mass spectrometry (LC-MS/MS), and, when necessary, qualitative identification of unknown substances using high-resolution mass spectrometry (HRMS). For death cases, comprehensive toxicological analysis must encompass multiple biological matrices, including blood, urine, vitreous fluid, gastric contents, and hair, to systematically determine the cause of death, clarify medication history, and analyze postmortem changes. Hair segmentation analysis has unique application value, reconstructing the medication timeline of the study subject several months prior to death, providing crucial technical support for case investigations.

Public safety screening scenarios (including workplace drug testing, drug rehabilitation monitoring, driving ability assessment, etc.) require the use of efficient, high-throughput, and cost-effective testing technologies and methods. Immunoassay methods, especially automated high-throughput detection platforms, occupy a core dominant position in such scenarios. In recent years, the application scope of oral liquid testing has become increasingly widespread due to its advantages such as the ability to achieve full visual monitoring of the sampling process and effectively avoid the risk of adulteration. The core challenge facing public safety screening is how to continuously update the detection panel to cover the emerging NPS, while controlling reasonable detection costs and achieving a balance between screening efficiency and cost control.

Drug epidemiology research requires comprehensive detection technologies and methods capable of accurately identifying and quantifying various NPSs and their metabolites. Wastewater analysis, as an emerging tool in drug epidemiology research, can assess community-level drug use characteristics and prevalence patterns by detecting drug residues in wastewater treatment plant influent. Liquid chromatography-high resolution mass spectrometry (LC-HRMS) is particularly suitable for such research scenarios because it enables efficient detection of non-target compounds and can even trace emerging NPS types and their usage. This type of epidemiological research can provide crucial data support for the scientific formulation of public health decisions and contribute to the further improvement of public health prevention and control systems.

4.3. Advances in Sample Pretreatment Technology

Sample pretreatment is one of the most challenging core steps in the analysis of NPS, and its effectiveness directly determines the sensitivity, selectivity, and reproducibility of the detection method. Liquid-liquid extraction (LLE) and solid-phase extraction (SPE), as traditional sample pretreatment techniques, can effectively enrich the target analyte and remove matrix interference. However, these methods generally have limitations such as cumbersome operation steps, long time consumption, and large consumption of organic solvents.

Microextraction techniques (such as solid-phase microextraction (SPME), liquid-phase microextraction (LPME), and dispersive liquid-liquid microextraction (DLLME) have demonstrated significant technical advantages in NPS analysis by reducing the amount of organic solvent used, simplifying the operation process, and improving enrichment efficiency. Among them, SPME technology integrates the extraction, enrichment, and sample introduction processes into a single step, making it particularly suitable for automated high-throughput analysis scenarios. A review article published in 2025 systematically summarized the latest research progress in synthetic cannabinoid sample pretreatment techniques, emphasizing the core role of microextraction technology in improving the "whiteness" of analytical methods (*i.e.*, balancing analytical performance, environmental friendliness, and practicality) [17].

Protein precipitation (PP), as the simplest sample pretreatment method, has regained attention in NPS analysis in recent years due to improvements in precipitant optimization (such as using acidified acetonitrile) and subsequent processing steps. In particular, when the PP method is coupled with ultra-high performance liquid chromatography-tandem mass spectrometry (UHPLC-MS/MS), the simplified PP processing procedure can effectively meet the technical requirements of most clinical and forensic testing applications.

Guided by the principles of Green Analytical Chemistry (GAC) and "White Analytical Chemistry" (WAC), an extension and complement of GAC concept which applies RGB color model to merge green (ecological) with red (analytical) and blue (practical) perspectives into the white [18], NPS sample pretreatment technology is steadily developing towards miniaturization, automation, and environmental friendliness. Novel sample pretreatment methods (such as magnetic solid-phase extraction (MSPE) and adsorption extraction techniques based on metal-organic frameworks (MOFs) effectively improve the overall sustainability of the NPS analysis process by employing recyclable materials and reducing organic solvent consumption.

5. Challenges and Future Prospects

5.1. Major Challenges of Current Detection Technologies

Although NPS detection technology has made significant progress in recent years, the field still faces many technical challenges due to the inherent characteristics of NPS and the limitations of detection techniques, as follows:

The diversity of chemical structures is the primary challenge currently facing NPS detection. NPS manufacturers continuously generate new structural variants by subtly modifying the parent compound, thereby circumventing legal regulations and the identification capabilities of existing detection methods. Taking synthetic cannabinoids as an example, their basic chemical structure consists of four parts: a core skeleton, a linker group, a substituted ring, and a side chain tail. Each structural part can be modified in various ways, theoretically leading to thousands of structural variants. Existing detection methods struggle to keep pace with the rapid evolution of NPS structures, especially immunoassays and standard-dependent chromatographic methods, which may exhibit complete lack of response or insufficient response signals for newly emerging structural analogs, resulting in missed detections.

The complexity of metabolism further increases the difficulty of detecting NPS. Most NPS undergo extensive *in vivo* metabolic transformations after entering the body, generating a variety of metabolites, some of which may have pharmacological activity or toxicity. For example, the synthetic cannabinoid JWH-018 can be metabolized in the human body to produce more than 20 metabolites, covering various types such as monohydroxylation, dihydroxylation, carboxylation, and glucuronide conjugates [6]. The detection of metabolites requires specific detection methods, and obtaining reference standards is far more difficult than obtaining the parent compound. Adding to the complexity, significant differences exist in metabolic pathways between different species (such as humans and laboratory animals), making it difficult to directly extrapolate metabolic data obtained from animal experiments to human sample analysis, further increasing the complexity of metabolite detection.

The extremely low concentration of NPS in biological samples places extremely high demands on the sensitivity of detection methods. Most potent NPSs (such as some NBOMe series compounds) have active doses in the microgram range, resulting in concentrations in biological samples (such as blood and urine) often ranging from pg/mL to low ng/mL. Effective detection of such low-concentration NPSs requires advanced sample pretreatment and enrichment techniques, as well as high-performance detectors, which significantly increases the cost and complexity of the analysis process. The concentration of NPSs in alternative biological matrices such as hair is even lower, further increasing the difficulty of detection.

The lack of reference materials severely limits the development and validation of NPS detection methods. For newly emerging NPS, commercially available pure reference materials are often unavailable, and obtaining metabolite standards and isotope internal standards is even more difficult. This scarcity of reference materials greatly hinders the development of detection methods and makes it difficult to effectively guarantee the accuracy of quantitative detection results. Currently, the academic community and regulatory agencies are working to establish a mechanism for sharing NPS reference materials (such as the EU Reference Material Laboratory Network), but the development and sharing of reference materials still lags behind the emergence of new NPS, failing to meet actual detection needs.

Analysis speed and throughput are crucial in clinical and forensic practice. In emergency medicine, rapid NPS results are essential to guide clinical decisions; forensic laboratories need to efficiently process large volumes of samples to improve case detection efficiency. However, current methods with the highest accuracy (such as LC-MS/MS) are typically slow, making them unsuitable for high-throughput testing. Rapid methods (such as immunoassays), on the other hand, suffer from limitations such as insufficient specificity and a tendency to produce false negatives or false positives. Achieving a balance between analysis speed and accuracy remains a persistent technical challenge in the field of NPS testing.

5.2. Technological Innovation and Future Directions

Addressing the aforementioned technical bottlenecks in NPS detection, NPS detection technologies are steadily developing towards high throughput, high sensitivity, wide coverage, and intelligent operation. The research and application of various novel detection technologies provide crucial technical support for overcoming existing limitations. Against this backdrop, the widespread adoption and application of high-resolution mass spectrometry (HRMS) will significantly improve the overall efficiency of NPS screening and qualitative identification. Compared to traditional tandem mass spectrometry, HRMS techniques (such as quadrupole-time-of-flight mass spectrometry (QTOF) and orbital trap mass spectrometry (Orbitrap) can accurately provide precise mass numbers and isotopic distribution characteristics of target compounds, laying a solid technical foundation for the efficient implementation of non-targeted screening techniques. Modern HRMS instruments can simultaneously complete three core tasks—targeted quantitative detection, suspected target screening, and non-targeted screening—in a single analysis cycle (as shown in Table 3), significantly expanding the coverage and efficiency of NPS detection. Retrospective analysis based on HRMS technology has unique academic and application value. When a novel NPS is discovered, reanalyzing previously archived detection data can clarify whether the novel substance was present in previously detected samples, providing scientific support for tracing the spread of novel NPS and improving prevention and control strategies.

Table 3. Panorama of HRMS analysis strategies: targeted, suspected and untargeted.

Contrast dimension	Target quantitative analysis	Suspected screening	Non-targeted screening
Core purpose	Accurate characterization and quantification of known compounds	Known substance found to be possible in the sample but without a standard	Explore and identify completely unknown compounds in samples
Are standard required	Yes, methods and validation must be established with standards	No, list of suspects built on database/literature	No, designed to discover substances without prior information
Data acquisition mode	Usually a targeted acquisition mode (such as PRM or SIM) can also be extracted from FullScan	Retrospective analysis based on FullScan data	Collecting holographic data with FullScan mode
Key analysis tools	Standard curve, retention time, feature extraction	Suspected list, exact mass matching, isotope simulation	Statistical analysis, Kendrick mass defects, molecular networks
Main application scenarios	Regulatory testing, quantification of contaminants, determination of clinical biochemical indicators	Environmental monitoring, non-target pesticide screening in food, drug impurity profiling	Discovery of novel contaminants, biomarker exploration, metabolomics

Continued

Confidence level (math.)	Level 1	Level 2 - 3	Level 3 - 5
Specific detection/confirmation criteria	- Retention times consistent with standards - Accurate mass number deviation < 5 ppm - Secondary spectra match the standards exactly - Limit of quantification, recovery, etc. in accordance with the requirements of method validation	Level 2: Secondary spectrum highly matched to database/literature with consistent retention time predictions Level 3: Exact mass and isotope matches only, or only compound classes can be inferred	Level 3: Same as above (exact mass and isotope match only, or inferred category) Level 4: Determination of unique molecular formula only Level 5: Only precise mass signature found (signature to be identified) - Subsequent synthesis of standards or final confirmation by NMR is required

While HRMS technology solidifies the foundation for accurate NPS detection, artificial intelligence (AI) and machine learning technologies have opened up new paths for efficiency improvement and proactive prevention in this field, demonstrating broad application potential and development space in NPS detection. AI algorithms can be used to accurately predict the mass spectrometry response behavior, *in vivo* metabolic pathways, and toxicological characteristics of novel NPS, thereby significantly shortening the R&D cycle of NPS detection methods and improving R&D efficiency. At the level of detection data analysis, machine learning models can assist in the accurate identification of trace NPS targets in complex matrices, effectively reducing the incidence of false positives and false negatives, and further improving the reliability of detection results. Furthermore, virtual screening platforms built based on cheminformatics and computational toxicology theories are currently under continuous R&D and optimization. Such platforms can achieve accurate prediction of the psychoactive potential of novel compounds, providing important technical support for the construction of early warning systems for NPS, and helping to achieve proactive prevention and control of novel NPS, forming an efficient and complementary detection pattern with HRMS technology.

Compared to the breakthroughs of HRMS and AI technologies in accurate laboratory detection and efficient analysis, the actual needs of on-site and personalized detection have driven the breakthrough development of microfluidics and lab-on-a-chip technologies. This technology integrates core operational units such as sample pretreatment, separation, and detection onto a microchip carrier, significantly reducing sample and reagent consumption, shortening the analysis cycle, and lowering the R&D and usage costs of detection instruments. In the future, portable NPS detection devices are expected to be miniaturized to the size of a smartphone, providing near-laboratory-level accuracy. These portable detection devices are particularly suitable for scenarios such as border inspection, music festival security monitoring, and emergency room on-site testing, effectively meeting the practical needs of various rapid on-site testing scenarios, further expanding the scenario coverage of NPS detection, improving the accuracy and efficiency of on-site testing, and filling the gap in portability inherent in traditional detection technologies.

Beyond expanding detection efficiency and application scenarios, the need for in-depth elucidation of NPS toxicological mechanisms and clinical translation has driven the application and development of multi-omics integrated analysis technologies. These technologies will elucidate the *in vivo* mechanisms of action and potential toxicological effects of NPS from a more systematic and comprehensive scientific perspective. In addition to accurately detecting NPS and its metabolites, systematic analysis of the dynamic changes in endogenous metabolites, proteins, and gene expression levels can reveal the toxicological mechanisms of NPS and screen for specific biomarkers related to NPS exposure. For example, metabolomics analysis can clarify the specific metabolic perturbation patterns induced by NPS, providing new targets and theoretical basis for the clinical diagnosis and targeted treatment of NPS poisoning. Currently, although these integrated analysis methods are mainly applied in basic research related to NPS, they are expected to gradually be transformed into clinically applicable technologies in the future, and, in conjunction with HRMS, AI, and other technologies, provide important theoretical and technical support for the clinical diagnosis and treatment of NPS-related poisoning diseases.

While various NPS detection technologies continue to iterate and upgrade, and their functions are constantly being improved, the global strategy of sustainable development and the trend of green chemistry have driven the research and application of green and sustainable analytical methods, forming a comprehensive and diversified development pattern for NPS detection technologies. NPS detection methods designed based on the principles of White Analytical Chemistry (WAC) can minimize the impact on the ecological environment and the consumption of various resources while ensuring that the analytical performance meets the standard requirements. Specific implementation paths include using environmentally friendly solvents to replace traditional organic solvents, optimizing experimental procedures to reduce experimental waste, and developing reusable, highly efficient adsorption materials. Future NPS detection methods not only need to possess advanced technical performance to meet actual detection needs but also need to consider environmental friendliness and social acceptability, ultimately achieving the synergistic advancement of NPS detection technology development and sustainable ecological environment development, aligning with the development concept of green analytical chemistry.

6. Conclusions

The rapid iteration and global spread of NPS pose an unprecedented threat to global public health security. These artificially designed, synthesized, and continuously structurally modified chemicals, with their structural diversity, pharmacological potency, and legal circumvention capabilities, continue to challenge the applicability and application boundaries of existing detection technologies. This article systematically reviews the classification characteristics, epidemiological status, and principles and applications of mainstream detection technologies for NPS, analyzes the technological progress in this field, and clarifies the core bottlenecks and shortcomings of the NPS detection system.

In the detection technology system, chromatography-mass spectrometry (especially LC-MS/MS and UHPLC-MS/MS) has become the gold standard for forensic and clinical toxicology testing due to its high sensitivity, high specificity, and broad coverage. Spectroscopic techniques, immunoassays, and emerging sensor technologies, with their advantages of speed and convenience, play an irreplaceable role in rapid on-site screening and large-scale initial screening for NPS. The combination of multiple technologies with detection strategies based on the characteristics of different biological matrices provides a systematic solution for comprehensive and accurate NPS detection.

However, NPS detection still faces multiple technical bottlenecks, mainly including rapid iteration of NPS structures, complex *in vivo* metabolism, extremely low concentrations of target substances in biological samples, and a lack of reference materials. These challenges are driving the iterative optimization of NPS detection technology towards high throughput, high sensitivity, wide coverage, and intelligence. New technologies such as HRMS, AI, microfluidic chips, and multi-omics integration are breaking through the limitations of traditional technologies and opening up new paths and technological paradigms for NPS detection.

Looking ahead, breakthroughs in NPS testing not only rely on continuous innovation in testing technology, but also require a sound regulatory framework, strengthened international collaboration, and the establishment of a standardized testing system. Through technological innovation, regulatory optimization, and multi-level social collaboration, we can effectively address the public health risks posed by NPS, build a comprehensive NPS prevention and control system, and protect public health from its harm.

Conflicts of Interest

The author declares no conflicts of interest regarding the publication of this paper.

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