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Monitoring the use of novel psychoactive substances in Australia by wastewater-based epidemiology

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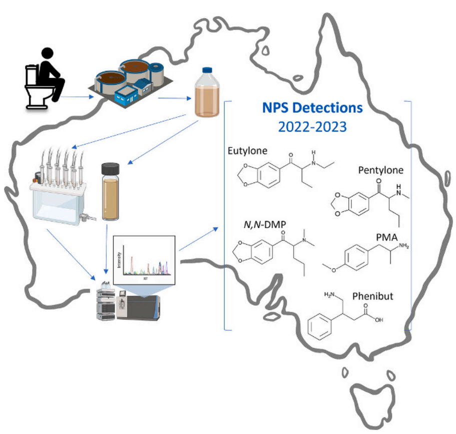
HIGHLIGHTS

- Wastewater samples collected in Australia were analysed for novel psychoactive substances (NPS)
- The most common NPS detected were pentylone, *N,N*-DMP, eutylone and phenibut
- Eutylone detections decreased whilst pentylone increased over the year
- Wastewater analysis is an early warning tool for alerting NPS use

GRAPHICAL ABSTRACT



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ABSTRACT

Users of novel psychoactive substances (NPS) are at risk, due to limited information about the toxicity and unpredictable effects of these compounds. Wastewater-based epidemiology (WBE) has been used as a tool to provide insight into NPS use at the population level. To understand the preferences and trends of NPS use in Australia, this study involved liquid chromatography mass spectrometry analysis of wastewater collected from Australian states and territories from February 2022 to February 2023. In total, 59 different NPS were included across two complementary analytical methods and covered up to 57 wastewater catchments over the study. The NPS detected in wastewater were 25-B-NBOMe, buphedrone, 1-benzylpiperazine (BZP), 3-chloromethcathinone, *N,N*-dimethylpentylone (*N,N*-DMP), *N*-ethylheptedrone, *N*-ethylpentylone, eutylone, 4F-phenibut, 2-fluoro deschloroketamine, hydroxetamine, mephedrone, methoxetamine, methylone, mitragynine, pentylone, phenibut, para-methoxyamphetamine (PMA), alpha-pyrrolidinovalerophenone (α-PVP) and valeryl fentanyl. The detection frequency for these NPS ranged from 3 % to 100 % of the sites analysed. A noticeable decreasing trend

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in eutylone detection frequency and mass loads was observed whilst simultaneously *N,N*-DMP and pentylone increased over the study period. The emergence of some NPS in wastewater pre-dates other sources of monitoring and provides further evidence that WBE can be used as an additional early warning system for alerting potential NPS use.

1. Introduction

Novel psychoactive substances (NPS) are compounds that are often analogues of drugs already in use. They are synthesised and sold as a 'new" drug alternative or added to other substances to alter the drug effect, sometimes without the user knowing (Victoria State Government Department of Health, 2023a; Victoria State Government Department of Health, 2023b). Potential harm associated with NPS use stem from there being minimal information on NPS doses, toxicity or longer-term health impact(s). Many NPS were collectively called :"legal highs" because early synthesised analogues were not classed as controlled or prohibited substances (United Nations Office on Drugs and Crime (UNODC), 2024). Australia is a Federation and some states/territories have adopted state-level blanket legislation to control NPS use while in others specific NPS are scheduled as they are identified (Grigg et al., 2020).

The use of NPS is necessarily less than "conventional" or mainstream illicit drugs, which makes it difficult to monitor and determine the extent of NPS use in the population (Sutherland et al., 2022a; Sutherland et al., 2022b). Seized material or voluntary drug testing can identify NPS being used intentionally or not. During periods of low availability of conventional stimulants, NPS or other adulterants were thought to be used as substitutes (Chen et al., 2011). Recently published Australian drug alerts confirm synthetic cathinones, particularly *N,N*-dimethylpentylone (*N,N*-DMP), were found in pills sold as MDMA and blood tests of people reporting use of MDMA or other stimulants (Victoria State Government Department of Health, 2023a; Victoria State Government Department of Health, 2023b). Additionally, chemical analysis of discarded drug packaging revealed that cathinone NPS were found with MDMA in at least one state in Australia (West et al., 2021). Forensic toxicology cases are one way to gauge current NPS circulating in the illicit drug market, unfortunately only after the harm has been done (Ferrari Júnior et al., 2022). Surveys of drug users provide another resource for estimating NPS use in Australia (Sutherland et al., 2022a; Sutherland et al., 2022b). Wastewater-based epidemiology (WBE) is another method which has been used to monitor the consumption of NPS worldwide (Bade et al., 2023a; Chen et al., 2023; Lee and Oh, 2023; Salgueiro-González et al., 2022). The current analytical capabilities of mass spectrometry enable the detection of compounds at low concentrations (sub ng/L range). Consequently, NPS use by even a small number of individuals or small quantities of drug consumed can be measured. Recent work has highlighted international NPS preferences of 3-methylmethcathinone, eutylone and mitragynine over the Christmas/New Year period by WBE (Bade et al., 2023a). Due to the constantly evolving nature of NPS use, routine monitoring can show drug use at any one time and give insight to how use spreads across areas over time. Additionally, early detection of NPS is best to provide warning to potential users and/or the healthcare sector that potentially harmful drugs could be found in wastewater before overdoses and fatalities occur. WBE can be used as an additional tool for alerting potential NPS use (Bade et al., 2019; Camilleri et al., 2021).

While previous studies have focussed on special events and holidays to increase the chances of detecting NPS in wastewater (Bade et al., 2023a; Bade et al., 2020a), this study aimed to evaluate which NPS are used in regular non-holiday periods throughout the year. This study aimed to detect and quantify temporal trends of NPS use from wastewater collected from up to 57 wastewater treatment plants across Australia from February 2022 for February 2023. Sampling for this study avoided public holidays and unusual events to determine trends in NPS use across the year. Two complementary methodologies were utilised – solid phase extraction as well as direct injection analysis – to provide an understanding of NPS use in Australia at the population level. Solid phase extraction (SPE) was performed to obtain a 1000-fold enrichment factor to enable the detection of compounds excreted at low concentrations. The use of SPE as a preparative concentration step in WBE improves the susceptibility for detection of compounds taken sporadically, in low quantities or by few users.

2. Methods

2.1. Reagents

Reference standards and their respective deuterated analogues (internal standards), where available, were purchased as certified solutions or powdered salts from Cerilliant (round rock, USA) and Toronto research chemicals (Toronto, Canada) (**Supplementary Table S1**). For analytes without a matched deuterated analogue, MDMA-d5 was used as a surrogate internal standard. Analytical grade methanol and formic acid were purchased from ThermoFisher scientific (Waltham, MA, USA)

2.2. Sample collection

Wastewater was collected from up to 57 treatment plants (20 capital city and 37 regional catchments where possible) from across Australia as a part of the National Wastewater Drug Monitoring Program (Australian Criminal Intelligence Commission, 2023a). Catchments were sampled from all states and territories in Australia; Australian Capital Territory (ACT), New South Wales (NSW), Northern Territory (NT), Queensland (QLD), South Australia (SA), Tasmania (TAS), Victoria (VIC) and Western Australia (WA). In accordance with the Program sampling protocol, state or territory capital city catchments were sampled for one week of 7 consecutive days every two months from February 2022 to February 2023, while all other sites (termed regional sites from here on in) were collected daily across a week every four months. The sites monitored for capital cities (20 sites) had coverage of 47.6 % of the Australian population for most collections, whilst the addition of the regional sites gave up to 57 % population coverage in total (Australian Criminal Intelligence Commission, 2023a; Australian Criminal Intelligence Commission, 2022a; Australian Criminal Intelligence Commission, 2022b; Australian Criminal Intelligence Commission, 2023b). Daily 24-hour composite influent wastewater was collected and sodium metabisulphite (0.5 g/L) or hydrochloric acid (to lower pH to 2) was added to each sample as preservative to prevent degradation of the compounds of interest (Bade et al., 2020b). The wastewater samples were stored at −20 °C for transport to laboratories at the University of South Australia and The University of Queensland and kept at −20 °C until processing and analysis.

2.3. Qualitative analysis

Solid phase extraction (SPE) using a previously validated method was performed on 100 mL of influent wastewater collected from capital city and regional sites across Australia during 2022 (Bade et al., 2020b). Briefly, the solid phase extraction involved pre-conditioning UCT™ XRADH cartridges (500 mg/6 mL) with methanol, followed by sodium acetate buffer (20 mM, pH 5). Wastewater was loaded under gravity then washed with sodium acetate buffer, then acetic acid (0.1 M) and finally methanol before eluting with a solution consisting of dichloromethane: isopropanol: 28 % ammonia (78:18:4). Samples were then dried under nitrogen and reconstituted with methanol (20 μL) followed by 0.1 % formic acid in water (80 μL). Data was expressed qualitatively, as many signals were identified as above limit of detection (signal to noise ratio ≥ 3) but below limit of quantitation (LOQ) (signal to noise ratio ≥ 10). If only one transition was found, the analyte was deemed detected but not confirmed. Instrumental blanks (water) were analysed throughout each batch to confirm there was no analyte carry over. Retention time of the analytes in wastewater samples matched certified reference material for every detected analyte (± 2 %). Quality control samples of NPS analytes spiked into wastewater followed by extracted was performed alongside every batch to monitor extraction recovery and performance and blank samples were analysed throughout to ensure there was no carry over. Where possible, deuterated analogues of NPS were also added to every sample to monitor sample variation and retention time (**Supplementary Table S1**). Every two months, 20 capital city sites were sampled, and up to 37 regional sites were sampled quarterly. Three samples, covering one weekday and both weekend days were extracted and analysed using a Sciex Triple Quad 6500+ LC-MS/MS by an analytical method that included 35 NPS compounds (**Supplementary Table S1).** For sites where no weekend samples were collected, for example, the 3 sites in TAS, three weekday samples were analysed.

2.4. Quantitative analysis

A validated direct injection, LC-MS/MS analysis method was used for the quantification of NPS in wastewater (Bade et al., 2023b). Wastewater samples from capital cities in Australia collected every two months were spiked with deuterated analogues and analysed after direct injection by a Sciex Triple Quad 7500 LC-MS/MS that included 33 NPS compounds (**Supplementary Table S1**). For confirmation and quantitation of NPS using this method, retention time was within 2 % of the reference standard and the presence of two transitions with an ion abundance ratio within 20 % was required. Quality control procedures were followed by the inclusion of procedural and instrumental blanks, calibration curve wastewater extracts and a standard spiked sample (500 ng/L) in every batch. 17 capital city sites were monitored each collection month. Sites from Western Australia were not included in the analysis. Two days corresponding to Saturday and Sunday were analysed. For sites where no weekend samples were collected, for example, the 3 sites in TAS, the days with reported highest levels of MDMA were analysed based on data from the National Wastewater Drug Monitoring Program (Australian Criminal Intelligence Commission, 2023a; Australian Criminal Intelligence Commission, 2022a; Australian Criminal Intelligence Commission, 2022b; Australian Criminal Intelligence Commission, 2023b).

2.5. Data analysis

The frequency of NPS detections was determined for the qualitative data and quantitative data combined. Frequency of detection was expressed as the percentage of sites with positive detections for capital city or regional sites. To convert concentrations to population-normalised mass loads for the quantitative analysis, the concentration measured in wastewater (ng/L) was multiplied by the daily influent flow rate for each catchment (megalitres, ML) and divided by the population that is serviced by the catchment (in 1000's) (Castiglioni et al., 2013). Daily flow rates were provided by the wastewater treatment plant operators or utilities. Population estimates were derived from data obtained in the Australian Census 2021. The data was expressed as the mass of drug per day per 1000 people (mg/day/1000 people).

3. Results and discussion

3.1. Qualitative detection frequencies

The use of SPE as a preparative concentration step in WBE improves the probability of detecting sporadically taken compounds, in low quantities or by few users. The number of sites with NPS detections after SPE and following direct injection is presented as a percentage of the total number of sites analysed for each specific drug (Table 1). As many detections of NPS using this method fell below the LOQ, data is expressed qualitatively.

A total of 20 different NPS were detected in the wastewater sampled across Australia (Table 1). Of the NPS detected, nine of those were found in both capital and regional sites (SPE method), six in capital city sites only (direct injection method) and another five across both methods. There was a greater detection frequency of NPS in capital city sites compared to the regions. This could be due to the direct injection method only capturing capital city sites. However, it may be due to a greater number of users or greater amounts of NPS used in capital cities.

The most frequently detected NPS measured were the stimulants eutylone (44 % mean in capital cities), pentylone (65 % mean in capital cities), *N,N*-DMP (60 % mean in capital cities), and para-methoxyamphetamine (PMA) (25 % mean in capital cities), as well as phenibut (72 % mean in capital cities). Pentylone is a suspected metabolite of *N,N*-DMP but is also a drug itself (Victoria State Government Department of Health, 2023a; Victoria State Government Department of Health, 2023b). Over the February 2022 to February 2023 period, there was a noticeable decrease in the detection frequency of eutylone (from 65 % to 30 % in capital cities) whilst *N,N*-DMP and pentylone increased (from 13 and 25 % respectively, to 100 % for both, shift in red intensity, Table 1). Apart from the synthetic cathinones, PMA was the only amphetamine NPS detected frequently in April 2022 (65 % detection frequency of capital city sites and 51 % for regional sites) as well as some sporadic detections in the months following. Phenibut was frequently detected in all collections in most of the capital city sites reaching up to 94 % of sites in February 2023 (Table 1).

Eutylone, pentylone and PMA were the only NPS detected frequently in regional parts of Australia (detection frequencies ranging from 8 to 59 %) (Table 1). Mephedrone, another cathinone, was detected in capital city sites across Australia but more sporadically, appearing in 4 of the collection periods out of the 7 in total. It was also confined to 2 states, (VIC and NSW) as opposed to eutylone and pentylone which were found across the country (**Supplementary Table S2**). Detections of eutylone and pentylone in regional sites mirrored the capital city temporal patterns over the year. Detections were mostly confined to a few different catchments (Supplementary Table S3). This highlights that NPS detections in wastewater tend to be unpredictable to some extent. Therefore, there is a need for expansive collections to improve the probability of find NPS in wastewater. Tasmania was the exception, where all three capital city sites in this state had detections of eutylone for all collection months (100 % detection frequency) (**Supplementary Table S2**).

The notable changes related mainly to the detection frequencies of eutylone and *N,N*-DMP/pentylone (Table 1). Over the collection period there was a substantial decrease in the detection frequency of eutylone highlighted further in Fig. 1. Of the 20 capital city sites analysed per collection, 65 % had eutylone detections in February 2022 followed by progressively lower detection frequency over the subsequent months, ending at 30 % a year later. In the case of pentylone, the first positive detections appeared in April 2022 in NSW, SA and VIC (**Supplementary Table S2**). Starting from a detection frequency of 25 % in April 2022, by December 2022, use had spread to all capital city sites (100 % detection frequency) (Fig. 1). In addition, pentylone was detected in regional sites for all collections increasing from an initial 14 % detection frequency in April 2022 to 59 % by December 2022 (Table 1). *N,N*-DMP, first appeared in February 2023 (13 % detection frequency of capital city

Table 1
NPS detections in Australian wastewater catchments from February 2022 to February 2023.

NPS	Location	Detection frequency (%)						
		Feb-22	Apr-22	Jun-22	Aug-22	Oct-22	Dec-22	Feb-23
Number of sites	C	20	20	20	20	20	20	20
	R	-	37	-	38	-	37	-
25-B-NBOMe#	C							5
	R	-		-		-		-
Buphedrone#	C			5				
	R	-		-		-		-
BZP#	C					5	20	
	R	-		-		-	19	-
N-ethylheptedrone*	C	5						
	R	-		-		-		-
N-ethylpentylone*	C	15	5					
	R	-		-		-	3	-
Eutylone*	C	65	50	35	50	40	40	30
	R	-	19	-	16	-	16	-
2-fluoro deschloroketamine*	C	5		5		10		
	R	-		-		-		-
Mephedrone#	C	20	30	15	30			
	R	-	5	-	3	-		-
Methoxetamine#	C					5		
	R	-		-		-		-
Methylone#	C						5	5
	R	-	3	-		-	3	-
Pentylone*	C		25	30	40	95	100	100
	R	-	14	-	21	-	59	-
PMA#	C		65	25	20	15	10	15
	R	-	51	-	8	-	11	-
α-PVP#	C			5	5	5	5	
	R	-	3	-		-		-
Valeryl fentanyl#	C							
	R	-	3	-		-		-
NPS	**Location**	**Feb-22**	**Apr-22**	**Jun-22**	**Aug-22**	**Oct-22**	**Dec-22**	**Feb-23**
Number of sites		**16**	**17**	**17**	**16**	**15**	**15**	**17**
3-chloromethcathinone^	C						7	
N,N-DMP^	C	13	24	29	88	87	80	100
4F-phenibut^	C			6	6	7	7	12
Hydroxetamine^	C			6				
Mitragynine^	C							12
Phenibut^	C	56	59	59	69	93	73	94

^NPS that were only included in the direct injection method and analysed capital city sites only, * NPS that were included in both methods, # NPS only included in the solid phase extraction method. C = capital city sites, R = regional sites, Blue = lower frequency of site detections and red = higher frequency of site detections. – indicates samples were not collected for this time period. BZP: 1-benzylpiperazine, PMA: para-methoxyamphetamine (PMA), α-PVP: Alpha-Pyrrolidinovalerophenone, ***N,N*-DMP**: ***N,N*-dimethylpentylone**.

sites analysed) (Table 1). As not all 20 capital city sites were monitored for this drug over the entire study period, only eutylone and pentylone are included in Fig. 1 to maintain a matched site comparison.

The results of this study suggest that a preference for eutylone diminished during 2022 and throughout the second half of the year pentylone detections increased, possibly marketed as an alternative cathinone NPS. This phenomenon of decreasing eutylone detections with subsequent pentylone increases has been reported in the United States (US). The US National Drug Early Warning system trend report shows a decrease in eutylone detections in biological samples and seized drug material from late 2021 to 2022 (Krotulski et al., 2023). Following the decrease in eutylone detections in the US over the 2022 period, ***N,N*-**DMP and pentylone, increased each quarter to a peak in the first few months of 2023 (Krotulski et al., 2023). In Australia, drug alerts for pentylone were reported in February 2023 related to increased hospitalisations (Victoria State Government Department of Health, 2023b) and multiple seizures of *N,N*-DMP by police throughout 2022 (Australian Federal Police, 2023). ***N,N*-**DMP and pentylone were detected in this wastewater study as early as February 2022 in some states (Table 1). As the wastewater detections preceded the adverse heath findings and reported drug seizures, this study demonstrates that WBE can provide additional early warning for NPS circulating in the illicit drug market,

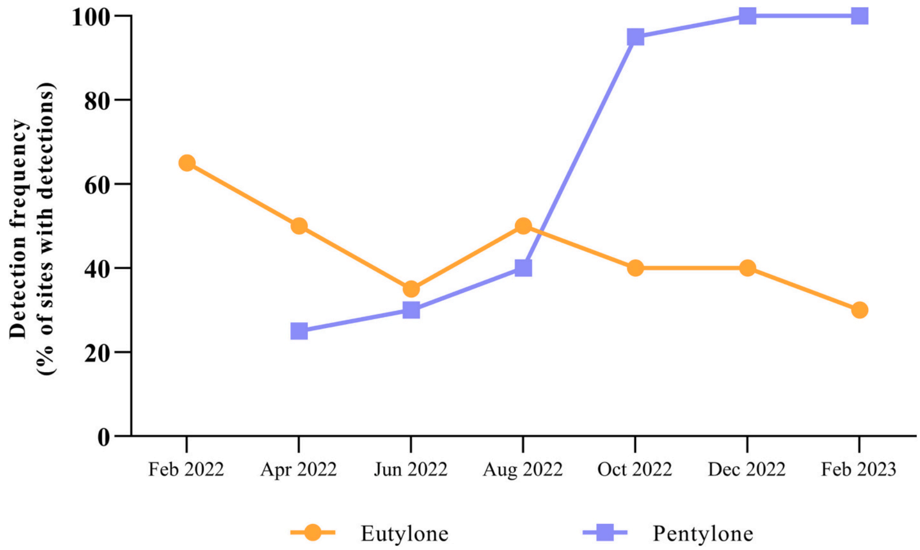

Fig. 1. Detection frequency of eutylone and pentylone following SPE of wastewater from capital city sites from February 2022 to February 2023. 20 capital city catchment sites from all states and territories monitored each collection month. Results are expressed as the percentage of sites analysed with positive detection of eutylone or pentylone for all state/territories combined.

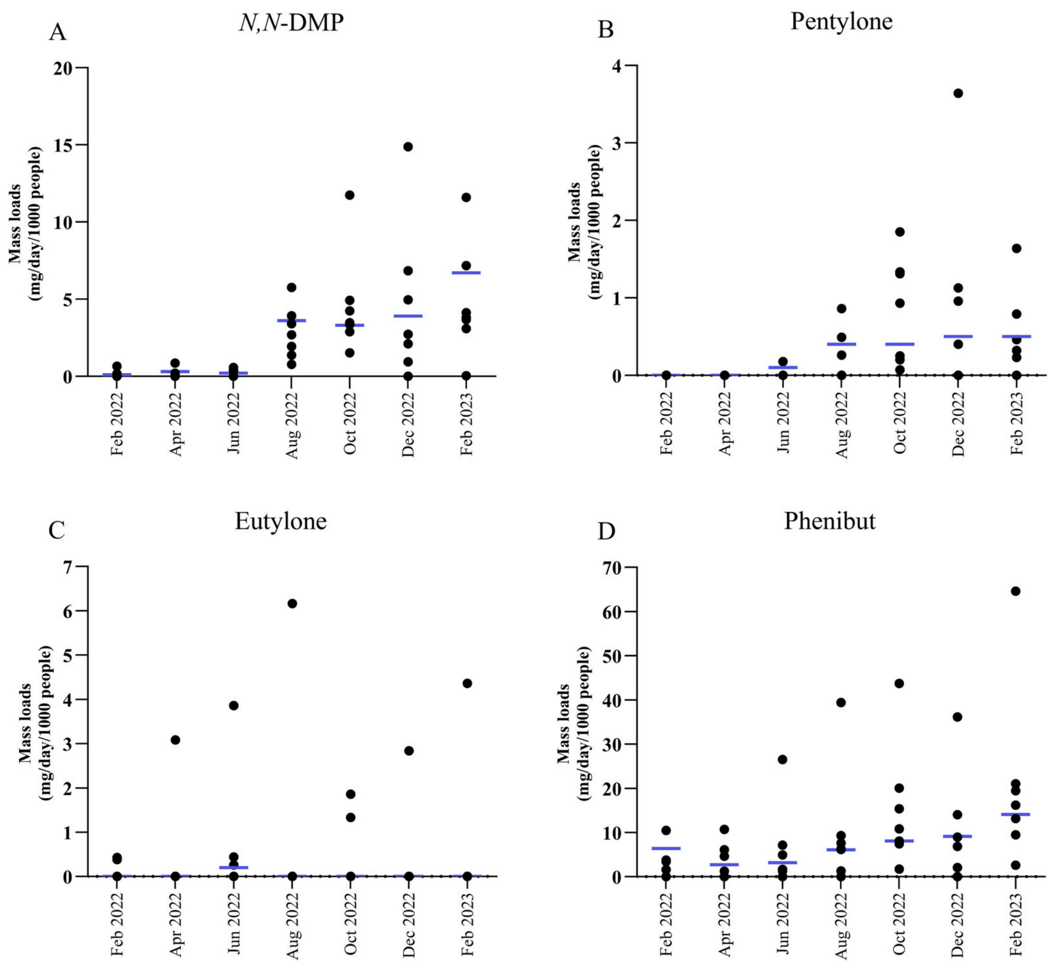

Fig. 2. Population normalised mass loads of NPS in Australia from February 2022 to February 2023 in wastewater following direct injection. A. *N-N*-dimethylpentylone, B. Pentylone, C. Eutylone, D. Phenibut. Between 15 and 17 capital city sites from all states and territories in Australia, except Western Australia were monitored each collection month with two days analysed (30–34 samples each collection). Each dot represents the average state or territory (7 included) population normalised mass load in mg/day/1000 people with the national population weighted average shown as a blue horizontal line.

possibly before hospitalisations or deaths occur due to their misuse. These types of findings have led to wastewater NPS data being incorporated into local drug early warning networks. For example, reporting on NPS detections in a timely manner in the South Australian Drug Early Warning System (SADEWS) (Camilleri et al., 2021).

3.2. Population-normalised mass loads (mg/day/1000 people)

Due to their higher abundance, the NPS including eutylone, pentylone, *N,N*-DMP and phenibut were quantifiable following direct injection and are reported as the average daily load. Both *N,N*-DMP (Fig. 2A) and pentylone (Fig. 2B) generally increased between February and December 2022, particularly for TAS, NSW and QLD with the highest loads observed in the October to February 2023 collections (Supplementary Figure s1). This was inconsistent with eutylone (Fig. 2C), seen exclusively in Tasmania at relatively constant levels (Supplementary Figure s1). The relative scale of use across different drugs cannot be determined when the wastewater data is presented as the daily mass load as excretion rates and known dose amounts are typically not available for NPS.

Phenibut is a neuropsychotropic drug with anxiolytic and nootropic effects when ingested (Owen et al., 2016). It is used recreationally for its euphoric effect and/or to reduce social anxiety (Owen et al., 2016). Phenibut is currently banned in Australia, with users usually purchasing the substance via internet outlets. Quantifiable levels of phenibut were measured in all states and territories in Australia in 2022 (Fig. 2D). The NT had the highest average excreted loads of all jurisdictions, meanwhile a large variation in the minimum and maximum excreted loads measured was observed for NSW (Supplementary Figure s1). Similar average excreted loads were observed for QLD compared to NSW, with infrequent detections in other states (TAS, ACT) or at lower levels (SA). There are few other reports of phenibut use in Australia, with 2 survey participants reporting use within the past 6 months in 2019, and one participant in 2021 (out of 797 and 794 participants total, respectively) (Sutherland et al., 2022a; Karlsson et al., 2021). There appeared to be an increasing trend in the excreted load of phenibut measured in wastewater across Australia during 2022 with the highest loads observed for the February 2023 collection (Fig. 2D). Prolonged use or misuse of phenibut can lead to dependency or tolerance that may lead to overdosing or undesirable side effects and/or withdrawal symptoms (Owen et al., 2016). With limited other sources that report phenibut use in Australia and worldwide, continual monitoring could be warranted to assess trends in use as well as providing a mechanism for early warning notifications, should levels continue to increase.

This study covered a variety of classes of NPS and include those known to be used currently both locally and internationally (Bade et al., 2023a; National Drug and Early Warning System (NDEWS) and Machine Perception and Cognitive Robotics (MPCR) Lab, 2022). Due to the evolving nature of NPS use, targeted analytical methods have limitations and may miss other drugs used by the population. Targeted methods may not be able to capture all NPS due to the inability to source new reference standards and the constant need to re-validate and update existing methods. Non-targeted methods using high resolution mass spectrometry to screen for other analytes may provide additional monitoring, but typically have lower sensitivity compared to targeted LC-MS methods.

4. Conclusion

This study provides evidence for the extent, duration, and amount of NPS used in Australia recently. The most frequently detected NPS in Australia throughout 2022 were eutylone, *N,N*-DMP, pentylone, PMA and phenibut. Detections of other NPS were mostly confined to the capital cities. Temporal monitoring revealed a decreasing trend of eutylone use, whilst *N,N*-DMP and pentylone increased over a similar timeframe. Synthetic cathinones can give similar effects to other recreationally used stimulants such as 3,4-methylenedioxymethamphetamine (MDMA) and/or have been found within MDMA formulations, often unknowingly to the user. Continued monitoring will reveal how long the preference for pentylone may last in Australia and also indicate other NPS consumption trend changes.

CRediT authorship contribution statement

Emma L. Jaunay: Writing – review & editing, Writing – original draft, Visualization, Formal analysis, Conceptualization. **Richard Bade:** Writing – review & editing, Supervision, Funding acquisition, Conceptualization. **Kara R. Paxton:** Writing – review & editing, Investigation. **Dhayaalini Nadarajan:** Writing – review & editing, Investigation. **Daniel C. Barry:** Writing – review & editing, Investigation. **Yuze Zhai:** Writing – review & editing, Investigation. **Benjamin J. Tscharke:** Writing – review & editing. **Jake W. O'Brien:** Writing – review & editing. **Jochen Mueller:** Writing – review & editing. **Jason M. White:** Writing – review & editing, Supervision, Funding acquisition. **Bradley S. Simpson:** Writing – review & editing. **Cobus Gerber:** Writing – review & editing, Visualization, Supervision, Resources, Funding acquisition.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Cobus Gerber reports financial support was provided by Drug and Alcohol Services South Australia. Cobus Gerber reports financial support was provided by Australian Criminal Intelligence Commission.

Data availability

Data will be made available on request.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.scitotenv.2024.170473.

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