

# ACMD

Advisory Council on the Misuse of Drugs

---

## **Nitrous Oxide– Updated Harms Assessment**

**March 2023**

## Contents

1. Introduction .....	3
Legal Status Under Drugs Legislation .....	3
Previous ACMD Advice .....	4
Other Relevant ACMD Advice .....	5
Aim of this Report .....	6
2. Legitimate Uses .....	7
Medical, Dental & Veterinary Uses .....	7
Food Sector .....	7
Fuel Additive .....	7
Academic Research.....	8
Other Uses .....	8
3. UK Prevalence & Patterns of Use .....	9
UK Prevalence.....	9
Regional Variations & Sociodemographic Differences.....	9
Prevalence at Festivals.....	9
Patterns of Use .....	10
4. Health and Social Harms .....	12
Physical Health Harms .....	12
Mortality .....	12
Poisonings .....	12
Neurological harms .....	13
Cardiovascular harms .....	15
Respiratory harms.....	15
Haematological harms .....	15
Reproductive harms .....	15
Dermatological harms .....	15
Genotoxicity .....	16
Psychological Health Harms .....	16
Intoxication.....	16
Psychosis, mood disorders and anxiety .....	16
Memory disorder .....	16
Dependence and addiction .....	17
Physical Health Harms to Others.....	17
Traffic.....	17
People in Treatment Services.....	18
Social harms to people using nitrous oxide .....	18

Loss of relationships .....	18
Social harms to others .....	18
Violence .....	18
Crime against others .....	19
Environmental damage .....	19
Impact on the Community .....	19
5. Public Call for Evidence Summary .....	20
6. Conclusions and Recommendations .....	22
7. References.....	37

## 1. Introduction

- 1.1. Nitrous oxide, also known as 'laughing gas', is a colourless, sweet-tasting gas discovered by Joseph Priestly in 1772.
- 1.2. Nitrous oxide (combined with oxygen) has been used as an anaesthetic and analgesic in medical and dental settings. Also, it has many other legitimate industrial and commercial uses, for example, as a food additive, propellant in catering and component of vehicle fuel.
- 1.3. Furthermore, nitrous oxide is the focus of pre-clinical and clinical research for a range of potential therapeutic uses, for example, as an acute antidepressant, as a treatment for alcohol withdrawal and as a potential intervention for post-traumatic stress disorder (PTSD).
- 1.4. For over 200 years nitrous oxide has also been used for its psychoactive effects. When inhaled nitrous oxide can produce euphoria, mild perceptual changes and uncontrollable laughter, which last for a short period of time (30 seconds to 1 minute). When used for non-medical purposes, nitrous oxide is commonly taken by inhalation directly from canisters or balloons/plastic bags containing the gas.
- 1.5. The precise mechanism of action is uncertain, but anaesthesia is widely believed to be due to inhibition of excitatory glutamatergic neurotransmission via non-competitive inhibition of N-methyl-D-aspartate (NMDA) receptors in the brain. NMDA receptor inhibition may also be responsible for euphoric and hallucinogenic effects (van Amsterdam et al., 2015).
- 1.6. The European Monitoring Centre for Drugs and Drug Addiction (EMCDDA) recently published an extensive review of nitrous oxide use. This included the current situation and responses to nitrous oxide use in several countries, including Denmark, Ireland, France, Lithuania, the Netherlands and Portugal (EMCDDA, 2022). Most countries have implemented measures to restrict the supply of nitrous oxide and provide targeted health promotion.

### Legal Status Under Drugs Legislation

- 1.7. Non-legitimate use of nitrous oxide is currently controlled under the Psychoactive Substances Act 2016 (PSA). This means the production, supply, and importation, but not possession (aside from in custodial settings) of nitrous oxide for its psychoactive effects is illegal. Under the Psychoactive Substances Act 2016 it is an offence to supply nitrous oxide if a person knows, or is reckless as to whether, it will be used for its psychoactive effects.
- 1.8. Nitrous oxide is not currently controlled under the Misuse of Drugs Act 1971.
- 1.9. To note, in this report we refer to use of nitrous oxide for its psychoactive effects as 'non-legitimate use'.

## Previous ACMD Advice

1.10. The ACMD report *Nitrous Oxide Abuse* (ACMD, 2015) concluded that the harmfulness of nitrous oxide as understood at the time did not warrant control under the Misuse of Drugs Act 1971.

1.11. In 2015 the ACMD made four recommendations, all of which were accepted by Government (see Table 1):

2015 Report Recommendations	Government Response
<p>i) <i>The Government to work with industry and retailers to better understand the supply chain, including areas of vulnerability, and to increase awareness with major retailers about the non-legitimate market to identify key features of misuse, such as bulk purchases and the combined sale of ‘crackers’ (which are used to dispense the gas from canisters).</i></p>	<ul style="list-style-type: none"> <li>• <i>Committed to working with industry and retailers: advice to retailers was produced and remains available. This includes advice on identifying and preventing sales to those who wish to use nitrous oxide for its psychoactive effects.<sup>1</sup></i></li> </ul>
<p>ii) <i>Local councils consider addressing anti-social behaviour (litter) associated with use of nitrous oxide through local court orders.</i></p>	<ul style="list-style-type: none"> <li>• <i>Local authorities had been given a range of tools and powers designed to tackle anti-social behaviour associated with psychoactive substances, which include powers for the police to confiscate nitrous oxide*</i></li> </ul> <p><i>*The ACMD understands these confiscation powers can be granted as part of Public Space Protection Orders (PSPOs) under the Anti-social Behaviour Act 2016</i></p>
<p>iii) <i>NHS PROTECT ensure that NHS Trusts and associated medical facilities are fully informed to the issue of misappropriation of medical gas cylinders using the recently published guidance. The guidance should be reviewed if misappropriation of medical gas cylinders continues to occur.</i></p>	<ul style="list-style-type: none"> <li>• <i>Provided guidance to NHS Trusts on the prevention of the theft of medical cylinders. This appears to have been at least partly effective, although there are problems in some parts of the country.</i></li> </ul>
<p>iv) <i>Department of Health to outline current audit processes in place that</i></p>	<ul style="list-style-type: none"> <li>• <i>NHS PROTECT recently introduced a self-assessment tool for healthcare</i></li> </ul>

<sup>1</sup> [Psychoactive Substances Act: guidance for retailers - GOV.UK \(www.gov.uk\)](https://www.gov.uk/government/guidance/psychoactive-substances-act-guidance-for-retailers)

<p><i>counter diversion and misuse in hospitals and other relevant medical settings.</i></p>	<p><i>providers to assess the security and governance arrangements of all medicines within their organisation to prevent and detect diversion and misuse. This tool takes the users through a review of activities that contribute to the overall security of medicines within the last 12 months and encompass most areas of medicines' governance. It may also be used to provide evidence of the robustness of medicine governance arrangements during the Care Quality Commission's inspection process. The tool was published on NHS PROTECT's website and circulated to all relevant stakeholders.</i></p> <p>The ACMD requested the Department of Health and Social Care (DHSC) for an update on the extent of current diversion of nitrous oxide from medical settings. Unfortunately, this update was not available at time of publication.</p>
--	--

**Table 1– ACMD 2015 Nitrous Oxide Report Recommendations and Government Responses**

### Other Relevant ACMD Advice

- 1.12. In 2022 the ACMD report *Drug Misuse Prevention Review* (ACMD, 2022a) considered how to prevent drug use among vulnerable groups of people. The recommendations from that report remain pertinent for all drugs, including nitrous oxide. It is particularly important not to use 'scare' tactics to try to reduce/deter use as the evidence suggested these, and additionally stand-alone mass media campaigns, are ineffective. Instead, other prevention methodologies for which there is robust evidence of effectiveness should be used.
- 1.13. In 2022 the ACMD also reported on young people's drug use (*ACMD vulnerable groups: young people's drug use* (ACMD, 2022b)). This report made several recommendations to Government around improving quantitative and qualitative data on young people's drug use and engagement with treatment services.

## Aim of this Report

- 1.14. In October 2021, the ACMD was commissioned by the then Home Secretary to conduct an updated health and social harms assessment of nitrous oxide and provide advice as to whether nitrous oxide should be controlled under the Misuse of Drugs Act 1971.<sup>2</sup> This commission cited the reported increased use by young people and the concern over the long-term effects caused by the inactivation of vitamin B12.
- 1.15. The ACMD received a subsequent commission on 7 February 2023 to expedite this review which sought advice on links between nitrous oxide use and anti-social behaviour, associated crime and impact on local communities and environmental impact.<sup>3</sup> In response to this supplementary commission the ACMD opened a two-week long rapid public call for evidence.
- 1.16. A dedicated ACMD working group compiled this review. Individuals were co-opted to the group based on their expertise and included representatives across academia, clinical neurology, law enforcement and the charity sectors. A full list of members can be found in Annex E. The working group reviewed the health and social harms of nitrous oxide in-line with the [Standard Operating Procedure for using evidence in ACMD reports](#).

---

<sup>2</sup> [HS letter to ACMD Chair - NO - 03 September 21.pdf \(publishing.service.gov.uk\)](#)

<sup>3</sup> [Nitrous Oxide – Updated Harms Assessment \(publishing.service.gov.uk\)](#)

## 2. Legitimate Uses

- 2.1. Nitrous oxide has many legitimate medical, commercial and industrial uses. The extent and scope of these uses in the UK is unclear, however they are estimated to be large. The following uses were highlighted in the 2015 ACMD advice and following engagement with the Home Office, Department for Environment, Food & Rural Affairs (DEFRA), Department for Business, Energy and Industrial Strategy (BEIS) as well as the recently published EMCDDA review (EMCDDA, 2022)

### **Medical, Dental & Veterinary Uses**

- 2.2. Nitrous oxide is used as an anaesthetic and analgesic in medical and dental settings. Also, nitrous oxide is used as an anaesthetic in veterinary contexts.
- 2.3. The manufacture and supply of medicinal products containing nitrous oxide is controlled by the Human Medicines Regulations 2012. The product requires a marketing authorisation and there are restrictions on who may buy and supply it.
- 2.4. If cylinders containing nitrous oxide are equipped with valves with an integrated pressure regulator, these device components are controlled according to the European Medical Device Regulation (Regulation (EU) 2017/745) and the UK Medical Devices Regulations 2002.

### **Food Sector**

- 2.5. Nitrous oxide is used as a food additive (E 942) and in a range of technological functions including as a propellant gas for whipping cream, packaging gas, foaming agent and antioxidant, and widespread use in catering.
- 2.6. Nitrous oxide can also be used as an extraction solvent, for example to remove caffeine from coffee to make decaffeinated coffee, extract fats, oils and specific proteins from raw ingredients.
- 2.7. The use of nitrous oxide as a food additive, component of foodstuffs, food ingredients or extraction solvent is controlled under retained EU legislation (retained EU Regulation 1333/2008, EU Regulation 1333/2008, Regulation 231/2012 and retained Directive 2009/32/EC).

### **Fuel Additive**

- 2.8. Nitrous oxide can be used as a component of rocket fuel and additive to fuels used in car racing. Nitrous oxide can also be used as a propellant in model rocketry.



## **Academic Research**

2.9. Nitrous oxide is also the focus of pre-clinical and clinical research for use as an acute antidepressant (Yan et al., 2022), treatment for alcohol withdrawal (Gillman et al., 2007) and treatment for post-traumatic stress disorder (PTSD) (Das et al., 2016). One response to the ACMD rapid public call for evidence also outlined there is currently academic research in the UK investigating the therapeutic benefits of nitrous oxide in treatment for PTSD.

## **Other Uses**

2.10. Nitrous oxide also has several other uses including as a refrigerant, leak detecting agent, oxidising agent, chemical reagent, in semiconductor manufacturing and as a component of electrical, electronic and optical equipment.

## 3. UK Prevalence & Patterns of Use

### UK Prevalence

- 3.1. According to the Office for National Statistics (ONS), reported nitrous oxide use in the last year in 16–59 year olds in England and Wales remained relatively stable between 2016–2020 (between 2.2–2.4%) and reduced to 1.3% in 2021–2022 (Office for National Statistics, 2022).
- 3.2. In comparison, 6.1% of 16–24 year olds reported using nitrous oxide in 2012–2013. Reported nitrous oxide use in 16–24 year olds peaked at 9.0% in 2016–2017. Between 2017–2020 reported nitrous oxide use in 16–24 year olds remained relatively stable between 8.7–8.8%. The first report after the pandemic, 2021–2022, reported nitrous oxide use in 16–24 year olds had reduced significantly to 3.9%.
- 3.3. The NHS Digital survey on smoking, drinking and drug use, which surveys secondary school pupils in England every two years (mostly 11–15 year olds), reported in 2016 and 2018 that 4.0% and 4.1% of pupils respectively used nitrous oxide. In 2021, this had fallen to 1.8% of pupils (Smoking, Drinking and Drug Use among Young People in England, 2021).
- 3.4. In England and Wales, nitrous oxide was the third most used drug in 2018, 2019 and 2020 after cannabis and cocaine. In 2017, the incidence was below that of cannabis and similar to that of cocaine. Between 2018 and 2020 reported use was slightly less than cocaine (Office for National Statistics, 2022).
- 3.5. In 2021 Scotland reported for the first time prevalence data on nitrous oxide use. In the past year, 3% of 16–24 year olds, 1% of 25–35 year olds and 1% of 35–44 year olds reported nitrous oxide use. Northern Ireland do not have publicly available data on prevalence of nitrous oxide use.

### Regional Variations & Sociodemographic Differences

- 3.6. There are no data on regional variations or sociodemographic differences in use across the UK. However, there are anecdotal accounts that nitrous oxide use may be becoming more prevalent in certain communities who are less likely to engage with other substances for religious or cultural reasons (for example communities where alcohol is not consumed on religious grounds). There are anecdotal reports that nitrous oxide use is increasing within some Muslim communities, especially amongst young people. Prevalence of use in these groups is not captured in official statistics.

### Prevalence at Festivals

- 3.7. Whilst festivals appear to be popular locations for nitrous oxide use, there is no evidence to suggest that overall usage amongst young adults at festivals has significantly increased year on year across the last decade. A bespoke analysis

for the working group found that nitrous oxide was commonly used alongside other drugs at festivals.

## Patterns of Use

3.8. Nitrous oxide can be inhaled using a face mask, balloon, plastic bag or releasing the gas into an enclosed space. Nitrous oxide can be stored in several forms:

- **Single-use finger-length metal cartridges** (also known as *bulbs*, *whippits*, *chargers* or *nangs*) which hold around 8g of gas. These cartridges are opened using a device known as a ‘cracker’, which can release the nitrous oxide into a balloon, or directly into the mouth, from which it is inhaled. Cartridges contain a small quantity of nitrous oxide and induce transient effects, meaning several cartridges may be used in a single session. One report highlighted over 17% of users reported using 25 or more cartridges in a single session (Kaar et al., 2016).
- **Larger canisters**, which typically contain 600g or 2kg of gas, are now being sold, deliberately targeting non-legitimate use. Anecdotal reports suggest the prevalence of these larger canisters has increased since 2015. The increase in use of large canisters as opposed to single-use cartridges may be due to larger canisters being cheaper per dose and more practical in filling balloons quickly (see Table 2).

Size of canister	Volume of gas	Equivalent number of balloons
8g	4.1 litres	2 small balloons
600g	305 litres	152 small balloons
2kg	1018 litres	500 small balloons

**Table 2– comparison of canister size, volume of gas and equivalent number of balloons.**

3.9. There is widespread availability of nitrous oxide from mainstream and specialist websites and other retail outlets. Nitrous oxide can be readily purchased at a low cost from online vendors, catering websites or other suppliers who exclusively sell nitrous oxide. Social media appears to be used extensively to advertise and sell nitrous oxide for non-legitimate use.

3.10. Some retailers and suppliers specifically sell to those who intend to use for non-legitimate purposes.

- Nitrous oxide may be packaged **with balloons, ‘crackers’ or vitamin B12 supplements.**
- There are reports of **‘flavoured’** nitrous oxide, although it is unclear if these have any legitimate uses.
- **Gas dispensers and related paraphernalia** continue to be sold by online retailers.

3.11. The extent to which these suppliers and retailers knowingly selling to those who intend non-legitimate use have been prosecuted under the Psychoactive Substances Act 2016 is unclear. According to the Home Office:

*In 2020, there were 31 convictions in England and Wales under the Psychoactive Substances Act 2016. There were 49 convictions in 2021. These included convictions related to nitrous oxide. The Crown Prosecution Service does not break down the number of cases involving nitrous oxide.*

3.12. The Crime Survey for England and Wales reported that in 2020-2021, 44.9% of 16– to 59 year olds who had used nitrous oxide, or a new psychoactive substance (NPS), had sourced this from ‘a friend, neighbour or colleague’. In comparison, 9.7% of 16–59 year olds who had used nitrous oxide, or a new psychoactive substance, had sourced this from ‘a shop’.

3.13. The definition of ‘heavy’ and ‘chronic’ use of nitrous oxide is not well established. There are no available data on the prevalence of or even a definition of what constitutes heavy or chronic use. From the point of view of diagnosis of chronic toxicity, as a guide daily use of 100 x 8g cartridges for at least a month could be considered ‘chronic’ use (Marsden et al., 2022).

## 4. Health and Social Harms

### Physical Health Harms

#### Mortality

- 4.1. The Office for National Statistics reported that over a two-decade period (between 2001 and 2020) there were 56 registered deaths involving nitrous oxide in England and Wales, 45 of these since 2010 (Office for National Statistics, 2022). These deaths include those that occurred in medical settings. There have been more deaths annually related to nitrous oxide in the last 8 years, compared to the 12 years before that. The highest annual numbers of registered deaths due to nitrous oxide were 8 in 2016 and 2019. This reduced to 6 in 2017, and 3 in both 2018 and 2020 (Office for National Statistics, 2022).
- 4.2. Scotland and Northern Ireland do not have publicly available data on deaths due to nitrous oxide use. There had not been informal or official reports of nitrous oxide related deaths through Northern Ireland's Drugs and Alcohol Monitoring and information System (DAMIS) or via the Drug Subgroup of the Organised Crime Taskforce (Department of Health in Northern Ireland). A bespoke analysis by the ACMD working group identified 3 deaths in Scotland and 1 death in Northern Ireland associated with nitrous oxide.
- 4.3. Deaths associated with the use of nitrous oxide occur due to secondary effects, rather than the direct toxic effect of the gas (EMCDDA, 2022). Reported causes of death include acute asphyxiation due to hypoxia, or, less commonly, sudden cardiac arrhythmia (Garakani et al., 2016). Deaths caused by hypoxia may occur when nitrous oxide is used in confined spaces, such as in a car or when using a face mask or plastic bag over the head (EMCDDA, 2022).
- 4.4. Deaths from traffic accidents associated with nitrous oxide have been mentioned as a possibility but thus far no specific cases have been reviewed globally (EMCDDA, 2022; Long, 2019).
- 4.5. There are currently no available UK data on the number of road traffic accidents associated with nitrous oxide use, or data on mortality from these. This is due to current difficulty with data recording and detection of these incidents.
- 4.6. While every drug-related death is a tragedy, the current number of annual deaths related to nitrous oxide remains low when compared to other drugs and comparable to other volatile compounds and solvents. In 2020 there were 3 deaths associated with nitrous oxide, 62 with benzodiazepines (Class C), 3 with solvents and 19 with fuels. Between 2001–2020, there were 56 deaths associated with nitrous oxide, 2,041 with benzodiazepines (Class C), 47 with solvents and 426 with fuels.

#### Poisonings

- 4.7. The National Poisons Information Service (NPIS) provides information and clinical advice to UK health professionals managing patients who may have been exposed to potentially toxic substances, including substances of misuse.

- 4.8. Annual numbers of enquiries to the NPIS from health professionals concerning nitrous oxide use received via its 24h telephone advice line have been increasing steeply in recent years. In 2018 there were 15 calls, in 2019 20 calls, in 2020 32 calls, 2021 38 calls and 2022 85 calls. For comparison, NPIS enquiries by fiscal year relating to all benzodiazepines were 185 in 2018–2019, 131 in 2019–2020, 138 in 2020–2021 and 79 in 2021–2022.
- 4.9. Of 132 nitrous oxide cases referred to the NPIS between 2011 and 2020, 54% were males and the overall mean age was 21.5 years old (range 13–38 years old). Three of 76 acute exposures resulted in fatality. Following reported chronic exposure (n=32) features most commonly reported were paraesthesia (n=13), hypoaesthesia (n=8), neuropathy (n=6), ataxia (n=6), headache (n=2) and dizziness (n=2) (Pucci et al., 2022).
- 4.10. The ACMD is aware that recent hospital admissions for solvents and inhaled anaesthetics (including nitrous oxide) have shown an increase between July to September 2022. However, no updated data were available in time for publication.

#### Neurological harms

- 4.11. Heavy use of nitrous oxide can lead to the inactivation of vitamin B12, thus reducing the activity of the B12-dependent enzyme methionine synthase (Thompson et al., 2015). This can lead to neurological disorders (as well as haematological disorders further discussed below). The effects of nitrous oxide on vitamin B12 were discussed in the 2015 ACMD report (ACMD, 2015).
- 4.12. Vitamin B12 deficiency caused by repeated nitrous oxide use can manifest itself as myeloneuropathy which is characterised by simultaneous damage of the tracts of the spinal cord and peripheral nerves (Lewis et al., 2021). There has been an apparent rise globally and in the UK of observed in cases of nitrous oxide-induced subacute combined degeneration of the spinal cord (Paris et al., 2023). This can cause serious and potentially permanent disability but is treatable if recognised early (Paris et al., 2023).
- 4.13. The most common early symptoms of neurological harms are tingling and numbness in the hands or feet (paraesthesia). These can occur acutely and transiently; however, symptoms can become persistent (EMCDDA, 2022). Other early symptoms include skin crawling, and later, staggering uncoordinated walk, lower limb weakness, muscles stiffening or tightening, overactive or overresponsive bodily reflexes such as twitching, bladder/bowel complaints of incontinence or retention and sexual dysfunction (Keddie et al., 2018; Paris et al., 2023; DrugWatch, 2022; EMCDDA, 2022).
- 4.14. People who repeatedly use nitrous oxide are at a dose-dependent risk of developing serious neurological consequences (Winstock & Ferris, 2020). Myeloneuropathy is associated with both longer term high-frequency use or high amounts of use over a short period of time (EMCDDA, 2022). One study of non-legitimate users found that the probability of reporting paraesthesia increased by 3.5% for every 10% increase in nitrous oxide dose per episode (Winstock & Ferris, 2020).

- 4.15. Non-legitimate users of nitrous oxide with pre-existing vitamin B12 deficiency may be more at risk of nitrous oxide induced myeloneuropathy. Populations at risk of developing vitamin B12 deficiency include vegetarians, vegans, and the elderly (Hannibal et al., 2016). Individuals with low folate stores may also be more susceptible (EMCDDA, 2022).
- 4.16. One case review study of patients in East London with neurological impairments caused by nitrous oxide use suggested an overrepresentation of cases within Asian ethnicities. This could be a result of underlying genetic, nutritional, or dietary predispositions to neurological damage, but could also be a result of circumstances predicating use. It is currently unknown whether different ethnic groups are more or less susceptible due to their B12 status and metabolism (Keddie et al., 2018).
- 4.17. New guidelines on clinical practice with regard to nitrous oxide have been published and endorsed by the Association of British Neurologists (Paris et al., 2023). Standard treatment involves cessation of nitrous oxide use alongside vitamin B12 supplementation (Thompson et al., 2015; Paris et al., 2023). Supplementation with vitamin B12 alone without cessation of nitrous oxide use appears to be ineffective at preventing neurological disorders due to the inactivation of the B12 supplements (Paris et al., 2023; EMCDDA, 2022). In a case series of four patients, neurological symptoms still occurred despite supplementation with oral and/or parenteral vitamin B12. It should be noted that these individuals were using 200 or more cartridges per day, and there is no information provided on the dose or route of the vitamin B12 supplementation used (Blair et al., 2019).
- 4.18. There are no readily available data on the number of patients undergoing treatment for neurological harms associated with nitrous oxide in the UK. However, the NHS has recently added SNOMED codes (specific clinical terms within electronic patient record systems) to record nitrous oxide use, which will enable this to be recorded in the future.
- 4.19. The Emergency Department/ Clinical Toxicology service at Guy's and St Thomas' NHS Foundation Trust has seen an increase in the number of presentations of individuals with peripheral neuropathy symptoms associated with chronic nitrous oxide use from 4 in 2020 to 7 in 2021 and 32 in 2022. The Royal London Hospital reported diagnosing and treating one case of nitrous oxide-induced subacute degeneration of the spinal cord on average every 9 days (Paris et al., 2023).
- 4.20. In France, of 126 cases reported to poison centres from 2017 onwards, 73 had sensory or motor problems. Paraesthesia was particularly common but problems with balance and walking were also reported. Balance and walking problems were especially common in people who were using the gas heavily for periods ranging from a few weeks to several years and varying from 50 cartridges in an evening to more than 600 cartridges a day (and some reporting more than one 0.56kg cylinder a day). Of these cases, five were hospitalised for neurological issues (EMCDDA, 2022).

4.21. In the Netherlands, 64 young adults were treated for a partial spinal cord injury caused by nitrous oxide use between 2018 and 2019 (EMCDDA, 2022).

#### Cardiovascular harms

4.22. Frequent and prolonged non-legitimate use of nitrous oxide has been associated with thromboembolic events (EMCDDA, 2022). The frequency of these events is currently unclear.

#### Respiratory harms

4.23. Nitrous oxide has limited respiratory depressant effects but may increase the respiratory depressant effects of other drugs if used at the same time (EMCDDA, 2022).

4.24. Inhaling nitrous oxide as a pressured gas from balloons in rare cases can lead to spontaneous damage to lung tissue, leading to a medically serious condition known as pneumomediastinum or pneumothorax where air leaks into the chest outside the lungs (EMCDDA, 2022). Based on a case report, there may be further potential for serious harm associated with combined use of MDMA and nitrous oxide (McDermott et al., 2015).

#### Haematological harms

4.25. Repeated exposure to nitrous oxide can lead to megaloblastic anaemia as a result of inactivation of vitamin B12 (EMCDDA, 2022; DrugWatch, 2022; Reynolds, 2006).

#### Reproductive harms

4.26. Before occupational measures such as maximum exposure limits for nitrous oxide were introduced, medical professionals in dental and midwifery practices, operating theatres and ambulance transport were exposed to high levels of nitrous oxide. Reported adverse reproduction effects included congenital anomalies, spontaneous abortion, and reduced fertility rates in females. Non-legitimate users may also be at risk if they exceed current health exposure limits. However, impaired reproduction in female non-legitimate users has not yet been reported and the risk for occasional users is likely to be limited (van Amsterdam & van den Brink, 2022). There have been anecdotal reports that some hospitals have discontinued the use of nitrous oxide because of concerns about occupational exposure but further data are currently unavailable.

#### Dermatological harms

4.27. The outer surface of nitrous oxide canisters can become freezing cold as the gas is discharged and contact with the skin or mucous membranes can cause acute soft tissue damage (commonly described as 'frostbite'). This is particularly the case with improper administration of the gas, including direct administration from tank to mouth (EMCDDA, 2022; Chan et al., 2018; Garakani et al., 2016; Hwang et al., 1996).

4.28. Soft tissue damage on the legs can occur if a tank is held between a person's thighs to secure it whilst filling a balloon. The person using nitrous oxide may



not notice the cold due to its analgesic action, which could result in more serious injuries (EMCDDA, 2022).

### Genotoxicity

4.29. Nitrous oxide-induced oxidative stress may lead to oxidative DNA damage (EMCDDA, 2022), based on studies of occupational exposure (Braz et al., 2020; Wrońska-Nofer et al., 2012; Wrońska-Nofer et al., 2009). Minimal DNA damage following short-term incidental use is likely to be repaired in people who are otherwise healthy and without genetic or environmental predisposition to increased risk of cancer, but this may not be the case for more frequent use. (EMCDDA, 2022).

## Psychological Health Harms

### Intoxication

4.30. Inhalation of nitrous oxide causes mild intoxication associated with euphoria and relaxation. There may be some distortion of sound. Feelings of anxiety and/or paranoia may also occur. These features generally last 1–2 minutes in the absence of further use.

### Psychosis, mood disorders and anxiety

4.31. The limited data available make it difficult to determine how many putative psychiatric sequelae are causally linked to nitrous oxide consumption. Other drug use and/or a history of mental illness makes the attribution of psychiatric symptoms to nitrous oxide use difficult (EMCDDA, 2022).

4.32. Psychiatric disorders have been reported in a small number of people who use nitrous oxide. Currently, most data are from case reports and case series, and it is difficult to estimate prevalence. In terms of associated psychiatric diagnoses, the most common is a psychotic episode (EMCDDA, 2022). Reported psychotic symptoms include delusions (often grandiose and/or paranoid), visual hallucinations, bizarre behaviour and mania, although the prevalence is unclear (Sethi et al., 2006; Garakani et al., 2014; Chen et al., 2018; Hew et al., 2018).

4.33. The psychosis associated with nitrous oxide use may resolve when usage is stopped and vitamin B12 deficiency is treated (Zheng, et al., 2020).

4.34. Other reported associated symptom profiles include panic attacks, anxiety, depression, lability of mood, and putative subtle personality changes (EMCDDA, 2022; Chen, et al., 2018; Alderman et al., 2000). Prevalence of these symptoms is unclear.

4.35. There have been reports of verbal aggression and suicidal ideation in some people using nitrous oxide (EMCDDA, 2022; Chen et al., 2018).

### Memory disorder

4.36. Heavy users of nitrous oxide have reported experiencing cognitive deficits including memory loss (EMCDDA, 2022; Van Atta, 2004). Prevalence of these symptoms is unclear.

## Dependence and addiction

- 4.37. The NMDA receptor, a receptor present throughout the brain and active in brain reward networks, is an important pharmacological target of nitrous oxide (see paragraph 1.5 for mechanism of action). Drugs active at the NMDA receptor have been shown to have a misuse potential and so this could be the case for nitrous oxide. Nitrous oxide may also cause changes in other neurotransmitters including dopamine (Sakamoto et al., 2006; Koyanagi et al., 2008), endogenous opioids and gamma-aminobutyric acid (GABA) (Sanders et al., 2008).
- 4.38. Whether nitrous oxide use causes dependence is uncertain (Sheldon et al., 2020), with some reports suggesting nitrous oxide does not seem to result in dependence and that evidence on the matter is anecdotal (van Amsterdam et al., 2015) while other reports suggest psychological dependence can develop (Ferreira et al., 2022).

## Physical Health Harms to Others

### Traffic

- 4.39. Driving whilst intoxicated with nitrous oxide could be dangerous due to greatly diminished neurocognitive and psychomotor capacities. Nitrous oxide is short acting and 30 minutes after use most behavioural, neurocognitive, and psychomotor functions return to normal. However, fatigue can be experienced 1 hour after nitrous oxide use (EMCDDA, 2022). The duration is likely to be dose dependent and may be longer for higher amounts of nitrous oxide. One report which evaluated driving skills after brief exposure to nitrous oxide found that errors increased and driving was impaired for up to 30 minutes after exposure (Moyes et al., 1979).
- 4.40. In some countries, an increase in traffic accidents involving nitrous oxide use has been reported (EMCDDA, 2022). For example, in the Netherlands, the number of incidents involving nitrous oxide and driving increased by 80% between 2019–2021 (2,652–4,860 incidents). Not all these incidents relate to driving while intoxicated; others relate to filling balloons while driving.
- 4.41. It is important to note that at present it is difficult to prove that a driver is under the influence of nitrous oxide due to its short-lived direct effects and general difficulty with detecting nitrous oxide in a driver's blood, urine, breath, or saliva. (EMCDDA, 2022).
- 4.42. A review of incidents in the city centre of Manchester found there had been 71 reported incidents in 2021-2022 of drivers inhaling balloons of nitrous oxide (in some cases while driving). This had increased from 31 incidents in 2020–2021 (DrugWatch, 2022).
- 4.43. As part of this review the ACMD sought evidence from the Department for Transport (DfT). Recording of cases of nitrous oxide influenced drug driving was difficult. Therefore, there are no data on nitrous oxide influenced drug driving and resulting harms that could be shared in this report.

- 4.44. A bespoke analysis by the ACMD working group suggested 20% of registered nitrous oxide deaths in the UK between 1971–2022 (15 deaths) were caused by road traffic accidents. Five of these deaths were identified as a driver in a fatal road traffic accident under the influence of nitrous oxide, and 9 deaths as a victim of a road traffic accident involving use of nitrous oxide by the driver.
- 4.45. Several responses to the ACMD public call for evidence highlighted there were some reports of driving whilst using nitrous oxide. However, there is no substantive evidence to comment on the extent of these harms in the UK.

### **People in Treatment Services**

- 4.46. Data from the National Drug Treatment Monitoring System (NDTMS) show that the number of people in treatment reporting problems with nitrous oxide is very low but has increased over the past 10 years, from 12 in 2013–2014 to 80 in 2020–2021.
- 4.47. The proportion of people in treatment citing nitrous oxide as the primary drug they use is low and is generally greatest within the 18–19 year olds and 20–24 year olds age ranges.
- 4.48. The number of young people (less than 18 years old) in treatment citing nitrous oxide as the primary drug they use is also low. This reached a peak of 27 patients in 2018-2019, then reducing to 19 patients in 2019–2020 and 6 patients in 2020–2021, before increasing to 11 patients in 2021–2022.
- 4.49. The number of people in treatment reporting use of nitrous oxide are significantly lower than benzodiazepines (Class C) (22,000 people in 2014–2015 and between 14,800–15,800 in 2018–2022) and lower than solvents (between 300–370 people from 2014–2022).

### **Social harms to people using nitrous oxide**

#### **Loss of relationships**

- 4.50. Social isolation is cited as a negative consequence of nitrous oxide use by professionals and frequent users (EMCDDA, 2022). Psychological and social consequences may have an impact on family or other personal and social relationships. However, it is not clear whether nitrous oxide use is the cause of users' "psychosocial problems" or whether these problems were pre-existing and contributed to the development of problematic use.

### **Social harms to others**

#### **Violence**

- 4.51. Given the large numbers of people who use nitrous oxide for non-legitimate use, there is little evidence to suggest that the vast majority are likely to become aggressive or violent.

### Crime against others

- 4.52. The European Crime Prevention Network (EUCPN) recommendation paper suggested there was little evidence on the involvement of criminal networks in the distribution of nitrous oxide (but suggested that limiting the legal sale of nitrous oxide may have the unintended consequence of the emergence of these) (EUCPN, 2021).
- 4.53. From the ACMD public call for evidence, there was no substantive evidence of links between nitrous oxide use and crime. One response reported a large seizure of nitrous oxide by the police, suggesting involvement of organised crime groups. Another response indicated that ease of supply, large markup and lower risk of possession or supply may make nitrous oxide attractive to criminal networks. Reports from local authorities and local enforcement revealed a mixed and limited picture.
- 4.54. There continue to be anecdotal reports of theft of nitrous oxide from hospitals.

### Environmental damage

- 4.55. The use of nitrous oxide is associated with litter of balloons/cartridges/chargers.
- 4.56. DEFRA does not collect any data on the extent to which nitrous oxide canisters are littered and they do not appear on national level surveys. In 2020, Keep Britain Tidy conducted a litter composition survey across England but littering of nitrous oxide canisters was not reported (Keep Britain Tidy, 2020).
- 4.57. For this review, DEFRA provided official emissions estimates for non-legitimate use of nitrous oxide, which are from the National Inventory forming part of the official carbon accounting system. Emissions for non-legitimate use were around 150 times lower than official uses as an anaesthetic, and far lower than for agriculture.
- 4.58. Nitrous oxide is not flammable but will support combustion to the same extent as oxygen. Used chargers and tanks are therefore likely to explode if thrown into fires (EMCDDA, 2022). The incorrect disposal of nitrous oxide canisters in mixed recycling bins could lead to canisters exploding when put through recycling facilities (DrugWatch, 2022).

### Impact on the Community

- 4.59. The use of nitrous oxide in public is associated with causing nuisance through littering of public spaces with balloons and cartridges and the hissing sound made when filling balloons (EMCDDA, 2022).
- 4.60. From the ACMD public call for evidence, there were some responses which suggested nitrous oxide use was associated with nuisance behaviour. There is no substantive evidence of links between nitrous oxide and anti-social behaviour. The responses also reported an evidence gap linking anti-social behaviour to nitrous oxide use and other drugs/ alcohol were considered more strongly associated with anti-social behaviour.

## 5. Public Call for Evidence Summary

5.1. The ACMD received 50 responses to the public call for evidence. A summary of responses is provided below, and further details can be found in Annex C:

Stakeholder	Number of Responses
Police	13
Local Authority	11
Charity / Voluntary Group	9
Member of Public / MP / Other	9
Legitimate User/ Business	5
Clinical Neurologist	3

**Table 3– stakeholder responses to the ACMD Public Call for Evidence**

5.2. Key themes which emerged from the rapid review of the public call for evidence included:

- Few submissions reported links between nitrous oxide use and anti-social behaviour. However, there were reports of an evidence gap and other drugs/ alcohol were suggested to have a greater association.
- There were no significant reports of nitrous oxide being associated with criminal networks and crime.
- Several submissions reported littering of nitrous oxide canisters in their local areas.
- Several submissions reported increased prevalence of larger canisters.
- Several submissions reported law enforcement had difficulty confiscating nitrous oxide from users. Several submissions reported nitrous oxide as not taking up a significant amount of police time.
- Several submissions reported long-term neurological harms associated with nitrous oxide use.
- Several local authorities had implemented Public Space Protection Orders (PSPOs) to tackle the issue of nitrous oxide use. Although no formal reviews have taken place, it has been reported that PSPOs had been successful.
- Several submissions reported examples of productive partnership working between the police, local authorities and charities using education and harm reduction initiatives.
- Several submissions suggested that education on the long-term health harms associated with nitrous oxide was needed.

- In addition to its use as an anaesthetic/ analgesic and in the food industry, several submissions reported widespread legitimate uses in research, rocketry, education and as a fuel additive.

## 6. Conclusions and Recommendations

The ACMD has come to the following recommendations, which should be considered by Government as a package of interventions. Approaches taken by Government and local authorities on other substances, food and medicines (for example sale of solvents, food crime, diverted and counterfeit medicines) should be explored in relation to nitrous oxide. Interventions should include:

- a. Additional measures to tackle non-legitimate supply.
- b. Educating the public and healthcare professionals on the immediate and long-term harms associated with nitrous oxide use.

No single recommendation on its own is likely to be sufficient to successfully reduce the harms associated with nitrous oxide use.

### 1. Legislation

Based on this harms assessment, the Psychoactive Substances Act 2016 remains the appropriate drug legislation to tackle supply of nitrous oxide for non-legitimate use. There is, however, a need for enforcement of the Psychoactive Substances Act 2016 to be supported by additional interventions designed to reduce health and social harms.

Based on this harms assessment, nitrous oxide should not be subjected to control under the Misuse of Drugs Act 1971 for the following reasons:

- a. *Level of health and social harms*: current evidence suggests that the health and social harms are not commensurate with control under the Misuse of Drugs Act 1971.
- b. *Proportionality of sanctions*: the offences under the Misuse of Drugs Act 1971 would be disproportionate for the level of harm associated with nitrous oxide and could have significant unintended consequences.
- c. *Impact on legitimate uses*: control under the Misuse of Drugs Act 1971 could produce significant burdens for legitimate medical, industrial, commercial, and academic uses. The current scale and number of legitimate uses that stand to be affected is unknown but is estimated to be large.

### Recommendation 1

Nitrous oxide should remain under the Psychoactive Substances Act 2016. Enforcement under the Psychoactive Substances Act 2016 should be supported by interventions in the following recommendations on tackling non-legitimate supply, monitoring and reducing health and social harms associated with nitrous oxide. Police forces should share examples of good practice in enforcement using the Psychoactive Substances Act 2016.

Lead– Home Office, Police Forces.

Measure of outcome– Nitrous oxide to remain under the Psychoactive Substances Act 2016. Sharing of good practice by Police forces.

## 2. Reducing Supply of Nitrous Oxide for Non-Legitimate Use

### Recommendation 2

The Home Office should work with other Government departments (and agencies) to understand and adopt successful approaches to tackling non-legitimate routes of supply, for example, in the regulation of food and medicines. Approaches should include:

- Restrictions on direct-to-consumer sales
- Restrictions on canister sizes that are not found to have legitimate uses
- Restrictions on the volume of sales that customers can purchase
- Restrictions on online sales including associated paraphernalia (for example 'crackers')
- Increased health warning information on packaging
- Closing down of websites selling nitrous oxide for non-legitimate uses

Lead– Home Office

Measure of outcome– Restrictions on sales of nitrous oxide for non-legitimate uses. Reduced availability of nitrous oxide, including from online vendors, for non-legitimate use. Health warning information on packaging.

## 3. Reduce Health Harms

The prevalence of nitrous oxide use remained stable between 2016–2020 and then reduced significantly following the pandemic period, as reported by official statistics. There are however increasing numbers of enquiries from health professionals to UK poisons centres. The number of people in treatment reporting problems with nitrous oxide is very low but has increased over the past 10 years.

While the number of deaths directly related to nitrous oxide remain low and few people approach drug treatment services requesting support with use of nitrous oxide, there has been a reported increase in neurological harms. These neurological harms may be associated with exceptionally heavy and persistent use of nitrous oxide.



### Recommendation 3

The ACMD recommends:

- a. Universal prevention activity focused on nitrous oxide. This should include education and harm reduction interventions aimed at the public, including young people and schools, around the immediate and long-term health effects associated with repeated and heavy nitrous oxide use. For example, there could be a national campaign which could utilise appropriate platforms such as social media.
- b. Information and advice should be made available to the public and in places where nitrous oxide use is more common (for example festivals). Organisations that already provide advice to the public should review this information to ensure it takes into account the most recently published information.
- c. Local authority public health teams should ensure they are connected to local policing, community safety and wider community concerns about the availability, prevalence and use of nitrous oxide in their areas, and ensure commissioned treatment services have the necessary information and resources to support individuals to reduce the risks and harms of nitrous oxide use.
- d. Dissemination of information and guidance to healthcare staff to increase awareness of harmful nitrous oxide use, its clinical consequences and appropriate treatment protocols. Organisations that already provide advice to health professionals should review this information to ensure it takes into account the most recently published information.

Lead– Department for Education, Office for Health Improvement and Disparities, Local Government Association, Association of Directors of Public Health, Chief Medical Officers in England, Wales, Scotland and Northern Ireland, National Poisons Information Service, FRANK.

Measure of outcome– The number of sessions, interventions and people reached with prevention activity. Dissemination of updated treatment protocols to clinical staff. Availability of information to the general public. Social media campaign uptake.

#### 4. Reduce Social Harms

There have been increased anecdotal reports that nitrous oxide is now being used while driving and that this use has contributed to road traffic accidents. It is currently difficult to meet the burden of proof for road traffic accidents involving nitrous oxide owing to challenges with testing. Currently there is also no specified limit and offence, which means police must rely on observational evidence.

There are several examples of partnership working across local authorities, charities and enforcement authorities. Although formal evaluations are limited, there is emerging evidence these partnerships have been effective in reducing the harms

associated with nitrous oxide. Existing powers available to local authorities, for example Public Space Protection Orders (PSPOs) in England and Wales, have been implemented infrequently but have been reported to be effective. Formal evaluation of these strategies is needed.

#### **Recommendation 4**

The ACMD recommends:

- a. Government, Police, Trading Standards and local authorities should explore further partnership working and use of existing powers under legislation other than the Psychoactive Substances Act 2016. These include, for example, Public Space Protection Orders (in England and Wales), Dispersal Notices and Community Protection Notices.
- b. Government undertake a review of local authorities that have introduced Public Space Protection Orders to take lessons from evaluations of different local approaches.
- c. Home Office and other Government departments to consider (including unintended consequences of) providing additional powers for Police to remove, confiscate and dispose of nitrous oxide canisters and paraphernalia from people using, or are intending to use nitrous oxide for non-legitimate purposes, including in a vehicle.
- d. Home Office and Department for Transport to explore how nitrous oxide could be added to existing drug/driving protocols, noting difficulties with roadside and forensic testing.

Lead– Home Office, Department for Levelling Up, Housing and Communities, Department for Transport, Police, Trading Standards, Local Government Association, Association of Directors of Public Health.

Measure of outcome– Use of other powers through partnership working, report on effectiveness of community interventions and increased use of those that have been successful, exploration of drug driving testing.

### **5. Monitoring to Understand Health and Social Harms**

At present there is no substantive evidence linking nitrous oxide with anti-social behaviour or widespread criminal activities. There are widespread reports of littering associated with nitrous oxide use however at present there is no substantive mechanism to monitor the environmental impact of littering associated with nitrous oxide use.

Evidence of prevalence of health harms, particularly neurological harms, are also limited. Up to date monitoring is needed.

## Recommendation 5

The ACMD recommends there should be enhanced long term data collection to better understand the health and social harms of nitrous oxide. This includes additional UK monitoring of:

- a. Type, prevalence and severity of neurological, neuropsychiatric, and psychological harms attributable to nitrous oxide.
- b. Number and type of anti-social behaviour incidents associated with nitrous oxide.
- c. Number of road traffic accidents associated with nitrous oxide use.
- d. Number of deaths in the UK associated with nitrous oxide use
- e. Mechanism to monitor the environmental impact of littering associated with nitrous oxide use.

Lead– Home Office, Department of Health and Social Care, Department for Environment, Food & Rural Affairs, Department for Transport.

Measure of outcome– Increased data on health and social harms.

## 6. Consultation on Legitimate Uses

Nitrous oxide has many legitimate medical, commercial and industrial uses. The extent and scope of these uses in the UK is unclear, however they are estimated to be large. A consultation with industry and academia will ensure that disproportionate burdens are not placed on legitimate uses.

## Recommendation 6

The Home Office should work with other Government departments (and agencies) and stakeholders to undertake a comprehensive consultation to develop an evidence base to fully understand the scope of legitimate uses for nitrous oxide. This consultation will also enable Government to identify non-legitimate routes of supply.

Such a consultation should fully determine:

- the potential impact(s) of any proposed legislative changes
- the full range of Government departments that could support action on other recommendations in this report
- legitimate supply routes, which would then identify non-legitimate routes of supply

Lead– Home Office.

Measure of outcome– Consultation with legitimate users.

## **7. Impact Review**

The ACMD requests a formal update from Government on the implementation of the 2015 recommendations in addition to a review of the impact of actions implemented following this report.

### **Recommendation 7**

The Home Office should design a framework for the assessment of the impact of any changes and undertake a formal evaluation of actions further to this advice and from the ACMD's 2015 advice to reduce the health and social harms associated with nitrous oxide use. This review should take place no sooner than three years after any actions are implemented.

Lead– Home Office.

Measure of outcome– Framework for the assessment of the impact of any changes; formal evaluation of actions three years after implementation.

## Annex A – List of Abbreviations used in this Report

<b>Abbreviation</b>	<b>Name</b>
ACMD	Advisory Council on the Misuse of Drugs
BEIS	Department for Business, Energy & Industrial Strategy
DAMIS	Drugs and Alcohol Monitoring and information System
DEFRA	Department for Environment, Food & Rural Affairs
DfE	Department for Education
DfT	Department for Transport
DHSC	Department of Health and Social Care
DLUHC	Department for Levelling Up, Housing and Communities
EMCDDA	European Monitoring Centre for Drugs and Drug Addiction
EUCPN	European Crime Prevention Network
FSA	Food Standards Agency
GABA	Gamma-aminobutyric Acid
MDA	Misuse of Drugs Act 1971
NDTMS	National Drug Treatment Monitoring System
NMDA	N-methyl-D-aspartate
NPIS	National Poisons Information Service
NPS	New Psychoactive Substance
OHID	Office for Health Improvement and Disparities
ONS	Office for National Statistics
PSA	Psychoactive Substances Act 2016
PSPO	Public Space Protection Order
PTSD	Post-Traumatic Stress Disorder
SOP	Standard Operating Procedure
SNOMED	Systematized Nomenclature of Medicine Clinical Terms

## Annex B- Quality of Evidence

### Range of evidence

Evidence gathered was considered in line with the ACMD's 'Standard Operating Procedure for using evidence in ACMD reports'. This report drew upon on:

- evidence from peer-reviewed literature (UK and international publications) particularly for consideration of health harms.
- data requests, submissions and guidance documents from Government Departments (and their agencies), and devolved administrations, including from:
  - Department for Business Energy and Industrial Strategy
  - Department for Environment, Food and Rural Affairs
  - Department of Health (Northern Ireland)
  - Department for Health and Social Care (including Office for Health Improvement and Disparities)
  - Department for Transport
  - Food Standards Agency
  - Home Office
- a rapid public call for evidence (between 8 February 2023 and 21 February 2023; 50 responses received).

### Quality of evidence

There was limited evidence on the long-term health harms associated with nitrous oxide.

There was anecdotal evidence on social harms, particularly on:

- Use of nitrous oxide in different communities
- Reports of changing use to larger multidose canisters
- Dependence
- Theft of nitrous oxide from hospitals
- Drug driving
- Prevalence of use.

There were no publicly available data on deaths in Scotland and Northern Ireland.

There were no UK data on number of road traffic incidents or data on mortality from these, owing to difficulty with data recording / detection of incidents.

There were no readily available data on the number of patients undergoing treatment for neurological harms associated with nitrous oxide in the UK.

The limited data available make it difficult to determine how many putative psychiatric sequelae are causally linked to nitrous oxide consumption.

Most data from psychiatric disorders are from case reports and case series.

There was no data on the extent to which nitrous oxide canisters are littered and they do not appear on national level surveys.

## Annex C- Summary of ACMD Public Call for Evidence

Question	Police (n=13)			Local Authority (n=12)			Charity/ Voluntary Group (n=9)			Clinical Neurologists (n=3)			Legitimate Use Trade Association/ Group (n=5)			MP/ Member of Public/ Other (n=9)		
	Yes	No	Blank	Yes	No	Blank	Yes	No	Blank	Yes	No	Blank	Yes	No	Blank	Yes	No	Blank
3a. Crime against others	3	8	2	5	7	0	1	6	2	1	2	0	2	2	1	2	5	2
3b. Community costs	3	8	2	8	4	0	3	4	2	1	2	0	1	3	1	2	5	2
3c. Environmental damage	7	1	5	9	3	0	5	3	1	2	1	0	2	2	1	6	1	2
3d. Developmental	0	10	3	2	10	0	3	4	2	2	1	0	1	2	2	1	6	2
3e. Dependence potential	5	6	2	6	6	0	4	2	3	1	1	1	1	2	2	2	5	2
3f. Accidents	4	7	2	3	9	0	5	2	2	1	2	0	1	3	1	1	6	2
4a. Physical health harms	6	5	2	6	5	1	3	3	3	3	0	0	1	3	1	0	6	3
4b. Psychological health harms	4	6	3	3	8	1	3	2	4	2	1	0	1	3	1	2	5	2
5. Aware of legitimate sale?	6	5	2	7	5	0	2	4	3	1	2	0	4	0	1	2	5	2
Aware of non-legitimate sale?	5	6	2	5	7	0	3	4	2	1	2	0	2	2	1	2	5	2
7a. Introduced PSPOs or similar?	1	10	2	3	9	0	1	5	3	1	2	0	0	4	1	2	3	4
7b. Evaluate effectiveness?	2	0	11	3	9	0	1	0	8	0	0	3	0	0	5	0	3	6
8a. Introduced other measures	5	5	3	10	2	0	5	3	1	1	2	0	3	1	1	1	3	5
8b. Evaluate effectiveness?	4	2	7	6	3	3	2	1	6	0	0	3	3	2	0	1	2	6
9a. Partnerships?	6	5	2	10	2	0	1	4	4	1	2	0	2	1	2	1	4	4
9b. Evaluate effectiveness?	3	3	7	8	3	1	1	0	8	0	1	2	0	1	4	0	2	7

## Annex D- ACMD Membership at Time of Publication

<b>Dr Ann Sullivan</b>	Consultant Physician in HIV and Sexual Health and National Co-lead for HIV Surveillance, Office for Health Improvement and Disparities
<b>Dr Anne Campbell</b>	Lecturer in Social Work, Queens University Belfast
<b>Dr Carole Hunter</b>	Lead Pharmacist, Alcohol and Drug Recovery Services NHS Greater Glasgow and Clyde and Doping Control Officer, UK Antidoping
<b>Professor David Taylor</b>	Director of Pharmacy and Pathology, South London and Maudsley NHS Foundation Trust; Professor of Psychopharmacology, Institute of Pharmaceutical Science, King's College, London; Honorary Professor, Institute of Psychiatry, Psychology and Neuroscience and Head of Pharmaceutical Sciences Clinical Academic Group, King's Health Partners
<b>Dr David Wood</b>	Consultant Physician and Clinical Toxicologist, Guys and St Thomas' NHS Trust and Honorary Reader, King's College London
<b>Dr Derek Tracy</b>	Consultant Psychiatrist and Medical Director, West London NHS Trust; Senior Lecturer, King's College London and Visiting Senior Lecturer, University College London
<b>Dr Emily Finch</b>	Clinical Director of the Addictions Clinical Academic Group and Consultant Psychiatrist for South London and Maudsley NHS Trust
<b>Professor Graeme Henderson</b>	Professor of Pharmacology, University of Bristol
<b>Mr Harry Shapiro</b>	Director, DrugWise



<b>Dr Hilary Hamnett</b>	Associate Professor in Forensic Science, University of Lincoln and Forensic Toxicologist
<b>Professor Judith Aldridge</b>	Professor of Criminology, University of Manchester
<b>Dr Kostas Agath</b>	Consultant Psychiatrist (Addictions), Change Grow Live Southwark
<b>Mr Lawrence Gibbons</b>	Head of Drug Threat (Intelligence Directorate, Commodities), National Crime Agency
<b>Mr Mohammed Fessal</b>	Chief Pharmacist, Change Grow Live
<b>Professor Owen Bowden-Jones</b>	Chair of Advisory Council on the Misuse of Drugs, Consultant psychiatrist, Central North West London NHS Foundation Trust and Honorary Professor, University College London
<b>Dr Paul Stokes</b>	Reader in Mood Disorders and Psychopharmacology, King's College London and Honorary Consultant Psychiatrist South London and Maudsley NHS Foundation Trust
<b>Mr Rob Phipps</b>	Retired, Department of Health, Social Services and Public Safety in Northern Ireland
<b>Dr Richard Stevenson</b>	Emergency Medicine Consultant, Glasgow Royal Infirmary
<b>Professor Roger Knaggs</b>	Associate Professor in Clinical Pharmacy Practice, University of Nottingham
<b>Ms Rosalie Weetman</b>	Public Health Lead (Alcohol, Drugs and Tobacco), Derbyshire County Council
<b>Professor Sarah Galvani</b>	Professor of Social Research and Substance Use, Manchester Metropolitan University

<b>Professor Simon Thomas</b>	Emeritus Professor of Clinical Pharmacology and Therapeutics, Newcastle University
<b>Professor Tim Millar</b>	Professor of Substance Use and Addictions, University of Manchester

## Annex E – ACMD Nitrous Oxide Working Group Membership

<b>Professor Roger Knaggs</b>	ACMD Member; Chair of ACMD Nitrous Oxide Working Group	Associate Professor in Clinical Pharmacy Practice, University of Nottingham
<b>Dr Ann Sullivan</b>	ACMD Member	Consultant Physician in HIV and Sexual Health and National Co-lead for HIV Surveillance, Office for Health Improvement and Disparities
<b>Dr David Wood</b>	ACMD Member	Consultant Physician and Clinical Toxicologist, Guys and St Thomas' NHS Trust and Honorary Reader, King's College London
<b>Dr Derek Tracy</b>	ACMD Member	Consultant Psychiatrist and Medical Director, West London NHS Trust; Senior Lecturer, King's College London and Visiting Senior Lecturer, University College London
<b>Professor Graeme Henderson</b>	ACMD Member	Professor of Pharmacology, University of Bristol
<b>Professor Judith Aldridge</b>	ACMD Member	Professor of Criminology, University of Manchester
<b>Dr Kostas Agath</b>	ACMD Member	Consultant Psychiatrist (Addictions), Change Grow Live Southwark
<b>Professor Simon Thomas</b>	ACMD Member	Emeritus Professor of Clinical Pharmacology and Therapeutics, Newcastle University

<b>Professor Alastair Noyce</b>	ACMD Co-opted Member	Professor in Neurology and Neuroepidemiology and Consultant Neurologist, Queen Mary University of London and Barts Health NHS Trust
<b>Mr Dan Gibbons</b>	ACMD Co-opted Member	Director, Re-Solv
<b>Professor Fiona Measham</b>	ACMD Co-opted Member	Chair in Criminology in the Department of Sociology, Social Policy & Criminology, University of Liverpool and Founding Director of The Loop Charity
<b>Professor Gino Martini</b>	ACMD Co-opted Member	Chief Executive Precision Health Technology Accelerator and Honorary Professor University of Birmingham, Reading University, Bradford University, King's College London, Anglia Ruskin University
<b>Dr Helgi Johannsson</b>	ACMD Co-opted Member	Consultant Anaesthetist, Imperial Healthcare NHS Trust & Vice President, Royal College of Anaesthetists
<b>Mr John Corkery</b>	ACMD Co-opted Member	Senior Lecturer in Pharmacy Practice at University of Hertfordshire
<b>Mr Mark Lay</b>	ACMD Co-opted Member	National Drugs Co-ordinator. NPCC/Home Office
<b>Professor Mark Pucci</b>	ACMD Co-opted Member	Consultant in Clinical Toxicology and Acute Medicine, University Hospitals Birmingham NHS Foundation Trust

<b>Dr Stephen Keddie</b>	ACMD Co-opted Member	Consultant neurologist, Barts Health NHS Trust
<b>Mr Peter Cain</b>	ACMD Co-opted Member	Drugs Scientific Advisor, Eurofins Forensic Services
<b>Mr Stephen Ream</b>	ACMD Co-opted Member	Director, Re-Solv

The ACMD would also like to thank those individuals and organisations who provided submissions as part of the public call for evidence.

## 7. References

ACMD (2015) ACMD advice on nitrous oxide abuse. London, Home Office, Advisory Council on the Misuse of Drugs. Available from: [ACMD advice on nitrous oxide abuse - GOV.UK \(www.gov.uk\)](https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/424242/ACMD_advice_on_nitrous_oxide_abuse_-_GOV.UK.pdf) [accessed 1 March 2023]

ACMD (2022a) Drug Misuse Prevention Review. London, Home Office, Advisory Council on the Misuse of Drugs. Available from: [Drug misuse prevention review - GOV.UK \(www.gov.uk\)](https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/1144242/Drug_misuse_prevention_review_-_GOV.UK.pdf) [accessed 1 March 2023]

ACMD (2022b) ACMD vulnerable groups: young people's drug use. London, Home Office, Advisory Council on the Misuse of Drugs. Available from: [ACMD vulnerable groups: young people's drug use - GOV.UK \(www.gov.uk\)](https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/1144242/ACMD_vulnerable_groups_young_people_s_drug_use_-_GOV.UK.pdf) [accessed 1 March 2023]

Alderman, C. P., & Nyfort-Hansen, K. (2000). Nitrous oxide abuse in a community setting: case report. *The Australian Journal of Hospital Pharmacy*, 30(3), 109-110.

Blair, C., Tremonti, C., Edwards, L., Haber, P. S., & Halmagyi, G. M. (2019). Vitamin B12 supplementation futile for preventing demyelination in ongoing nitrous oxide misuse. *The Medical Journal of Australia*, 211(9), 428-428.

Braz, M. G., Carvalho, L. I., Chen, C. Y. O., Blumberg, J. B., Souza, K. M., Arruda, N. M., ... & Braz, L. G. (2020). High concentrations of waste anesthetic gases induce genetic damage and inflammation in physicians exposed for three years: A cross-sectional study. *Indoor Air*, 30(3), 512-520.

Chan, S. A., Alfonso, K. P., & Comer, B. T. (2018). Upper aerodigestive tract frostbite from inhalation of automotive nitrous oxide. *Ear, Nose & Throat Journal*, 97(9), E13-E14.

Chen, T., Zhong, N., Jiang, H., Zhao, M., Chen, Z., & Sun, H. (2018). Neuropsychiatric symptoms induced by large doses of nitrous oxide inhalation: a case report. *Shanghai Archives of Psychiatry*, 30(1), 56.

Das, R. K., Tamman, A., Nikolova, V., Freeman, T. P., Bisby, J. A., Lazzarino, A. I., & Kamboj, S. K. (2016). Nitrous oxide speeds the reduction of distressing intrusive memories in an experimental model of psychological trauma. *Psychological medicine*, 46(8), 1749-1759.

DrugWatch (2022) Nitrous Oxide (N<sub>2</sub>O) A briefing for professionals. Available from: [N2O-briefing-for-professionals-v1.0-DrugWatch-version.pdf \(michaellinnell.org.uk\)](https://www.michaellinnell.org.uk/wp-content/uploads/2022/03/N2O-briefing-for-professionals-v1.0-DrugWatch-version.pdf) [accessed 1 March 2023]

EMCDDA (2022) Recreational use of nitrous oxide — a growing concern for Europe. Available from: [Recreational use of nitrous oxide — a growing concern for Europe | www.emcdda.europa.eu](https://www.emcdda.europa.eu/press-releases/2022/03/recreational-use-of-nitrous-oxide-a-growing-concern-for-europe) [accessed 1 March 2023]

EUCPN (2021) Recommendation paper: Preventing the misuse of nitrous oxide. Available from: [2101 Preventing the misuse of nitrus oxide ENG LR 0.pdf \(eucpn.org\)](https://www.eucpn.org/wp-content/uploads/2021/03/2101-Preventing-the-misuse-of-nitrus-oxide-ENG-LR-0.pdf) [accessed 1 March 2023]

Ferreira, P. M., Winstock, A. R., Schlag, A. K., Brandner, B., Henderson, G., Miller, I., ... & Nutt, D. (2022). A comparative study of the harms of nitrous oxide and poppers using the MCDA approach. *Drug science, policy and law*, 8, 20503245221127301.

Garakani, A., Jaffe, R. J., Savla, D., Welch, A. K., Protin, C. A., Bryson, E. O., & McDowell, D. M. (2016). Neurologic, psychiatric, and other medical manifestations of nitrous oxide abuse: a systematic review of the case literature. *The American journal on addictions*, 25(5), 358-369.

Gillman, M. A., Lichtigfeld, F., & Young, T. (2007). Psychotropic analgesic nitrous oxide for alcoholic withdrawal states. *Cochrane Database of Systematic Reviews*, (2).

Hannibal, L., Lysne, V., Bjørke-Monsen, A. L., Behringer, S., Grünert, S. C., Spiekerkoetter, U., ... & Blom, H. J. (2016). Biomarkers and algorithms for the diagnosis of vitamin B12 deficiency. *Frontiers in molecular biosciences*, 27.

Hew, A., Lai, E., & Radford, E. (2018). Nitrous oxide abuse presenting with acute psychosis and peripheral neuropathy. *Australian & New Zealand Journal of Psychiatry*, 52(4), 388-388.

Hwang, J. C. F., Himel, H. N., & Edlich, R. F. (1996). Frostbite of the face after recreational misuse of nitrous oxide. *Burns*, 22(2), 152-153.

Kaar, S. J., Ferris, J., Waldron, J., Devaney, M., Ramsey, J., & Winstock, A. R. (2016). Up: The rise of nitrous oxide abuse. An international survey of contemporary nitrous oxide use. *Journal of psychopharmacology*, 30(4), 395-401.

Keddie, S., Adams, A., Kelso, A. R., Turner, B., Schmierer, K., Gnanapavan, S., ... & Noyce, A. J. (2018). No laughing matter: subacute degeneration of the spinal cord due to nitrous oxide inhalation. *Journal of neurology*, 265, 1089-1095.

Keep Britain Tidy (2020) Litter Composition Analysis - Summary Report. Available from: [20200330 KBT Litter Composition Report - FINAL.pdf \(keepbritaintidy.org\)](#) [accessed 1 March 2023]

Koyanagi, S., Himukashi, S., Mukaida, K., Shichino, T., & Fukuda, K. (2008). Dopamine D2-like receptor in the nucleus accumbens is involved in the antinociceptive effect of nitrous oxide. *Anesthesia & Analgesia*, 106(6), 1904-1909.

Lewis, B., Nelson, G., Vu, T., & Judge, B. (2021). No laughing matter—Myeloneuropathy due to heavy chronic nitrous oxide abuse. *The American Journal of Emergency Medicine*, 46, 799-e1.

Long H (2019). Inhalants. Nelson L.S., & Howland M, & Lewin N.A., & Smith S.W., & Goldfrank L.R., & Hoffman R.S.(Eds.), *Goldfrank's Toxicologic Emergencies*, 11e. McGraw

Hill. <https://accesspharmacy.mhmedical.com/content.aspx?bookid=2569&sectionid=210260247>

Marsden, P., Sharma, A. A., & Rotella, J. A. (2022). Clinical manifestations and outcomes of chronic nitrous oxide misuse: A systematic review. *Emergency Medicine Australasia*, 34(4), 492-503.

McDermott, R., Tsang, K., Hamilton, N., & Belton, M. (2015). Recreational nitrous oxide inhalation as a rare cause of spontaneous pneumomediastinum. *Case Reports*, 2015, bcr2015209750.

Moyes, D.,\* Cleanton-Jones, P.\*\* & Lelliot, J. (1979). Evaluation of driving skills after brief exposure to nitrous oxide. *South African Medical Journal*, 56(23), 1000-1002.

NHS Digital (2021) Smoking, Drinking and Drug Use among Young People in England. Available at: [Smoking, Drinking and Drug Use among Young People in England, 2021](#) [accessed 1 March 2023]

Office for National Statistics (2022) Deaths related to volatile substances, helium and nitrogen in England and Wales: 2001 to 2020 registrations. Available here: [Deaths related to volatile substances, helium and nitrogen in England and Wales - Office for National Statistics \(ons.gov.uk\)](#) [accessed 1 March 2023]

Office for National Statistics (2022) Drug misuse in England and Wales: year ending June 2022. Available here: [Drug misuse in England and Wales: year ending June 2022](#) [accessed 1 March 2023]

Paris, A., Lake, L., Joseph, A., Workman, A., Walton, J., Hayton, T., ... & Noyce, A. J. (2023). Nitrous oxide-induced subacute combined degeneration of the cord: diagnosis and treatment. *Practical Neurology*.

Pucci, M., Moyns, E., Jutley, G., Crisp, R., Sandilands, E., Gray, L., ... & Bradberry, S. (2022). Recreational nitrous oxide abuse: Trends in enquiries to the UK National Poisons Information Service, 2011-2020. *British Journal of Clinical Pharmacology*.

Reynolds, E. (2006). Vitamin B12, folic acid, and the nervous system. *The lancet neurology*, 5(11), 949-960.

Sanders, R. D., Weimann, J., Maze, M., Warner, D. S., & Warner, M. A. (2008). Biologic effects of nitrous oxide: a mechanistic and toxicologic review. *The Journal of the American Society of Anesthesiologists*, 109(4), 707-722.

Sakamoto, S., Nakao, S., Masuzawa, M., Inada, T., Maze, M., Franks, N. P., & Shingu, K. (2006). The differential effects of nitrous oxide and xenon on extracellular dopamine levels in the rat nucleus accumbens: a microdialysis study. *Anesthesia & Analgesia*, 103(6), 1459-1463.



Sethi, N. K., Mullin, P., Torgovnick, J., & Capasso, G. (2006). Nitrous oxide “whippit” abuse presenting with cobalamin responsive psychosis. *Journal of Medical Toxicology*, 2, 71-74.

Sheldon, R. J., Reid, M., Schon, F., & Poole, N. A. (2020). Just say N<sub>2</sub>O—nitrous oxide misuse: essential information for psychiatrists. *BJPsych Advances*, 26(2), 72-81.

Thompson, A. G., Leite, M. I., Lunn, M. P., & Bennett, D. L. (2015). Whippits, nitrous oxide and the dangers of legal highs. *Practical neurology*, 15(3), 207-209.

van Amsterdam, J., & van den Brink, W. (2022). Nitrous oxide–induced reproductive risks: Should recreational nitrous oxide users worry?. *Journal of Psychopharmacology*, 36(8), 951-955.

van Amsterdam, J., Nabben, T., & van den Brink, W. (2015). Recreational nitrous oxide use: prevalence and risks. *Regulatory toxicology and pharmacology*, 73(3), 790-796.

Van Atta, R. E. (2004). Cognitive Impairment Associated with Habitual NITROUS OXIDE ABUSE. *Forensic Examiner*, 13(4).

Winstock, A. R., & Ferris, J. A. (2020). Nitrous oxide causes peripheral neuropathy in a dose dependent manner among recreational users. *Journal of Psychopharmacology*, 34(2), 229-236.

Wrońska-Nofer, T., Palus, J., Krajewski, W., Jajte, J., Kucharska, M., Stetkiewicz, J., ... & Rydzyński, K. (2009). DNA damage induced by nitrous oxide: study in medical personnel of operating rooms. *Mutation Research/Fundamental and Molecular Mechanisms of Mutagenesis*, 666(1-2), 39-43.

Wrońska-Nofer, T., Nofer, J. R., Jajte, J., Dziubałtowska, E., Szymczak, W., Krajewski, W., ... & Rydzyński, K. (2012). Oxidative DNA damage and oxidative stress in subjects occupationally exposed to nitrous oxide (N<sub>2</sub>O). *Mutation Research/Fundamental and Molecular Mechanisms of Mutagenesis*, 731(1-2), 58-63.

Yan, D., Liu, B., Wei, X., Ou, W., Liao, M., Ji, S., ... & Zhang, Y. (2022). Efficacy and safety of nitrous oxide for patients with treatment-resistant depression, a randomized controlled trial. *Psychiatry Research*, 317, 114867.

Zheng, R., Wang, Q., Li, M., Liu, F., Zhang, Y., Zhao, B., ... & Li, W. (2020). Reversible Neuropsychiatric Disturbances Caused by Nitrous Oxide Toxicity: Clinical, Imaging and Electrophysiological Profiles of 21 Patients with 6–12 Months Follow-up. *Neuropsychiatric Disease and Treatment*, 2817-2825.