Australian Government
Department of Health
Therapeutic Goods Administration

Notice of interim decision to amend (or not amend) the current Poisons Standard

TGA Health Safety Regulation

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Contents

1 Notice of interim decisions made under Regulation 42ZCZN of the *Therapeutic Goods Regulations 1990*

This web publication constitutes a notice for the purposes of regulation 42ZCZP of the *Therapeutic Goods Regulations 1990* (the **Regulations**). In accordance with regulation 42ZCZP, this notice sets out:

- the interim decisions made by a delegate of the Secretary under regulation 42ZCZN in relation to proposed amendments to the current Poisons Standard which were referred to an expert advisory committee under subdivision 3D.2 of the Regulations in March 2021;
- the proposed date of effect of the proposed amendments (in circumstances where the interim decision proposes an amendment to the current Poisons Standard).

In accordance with regulation 42ZCZP, interested persons (including the applicant requesting the amendment) are invited to make submissions to the Secretary in relation to these interim decisions on or before **27 August 2021**.

We have changed the way to make submissions.

Submissions should now be provided through our consultation hub. Submissions will be considered by the Delegate in making the final decision.

Please note that in accordance with subregulation 42ZCZQ(4) of the Regulations, the Secretary must publish all relevant submissions received, unless the Secretary considers the information to be confidential information.

2 Interim decision on a proposed amendment referred to the Advisory Committee on Medicines and Chemicals Scheduling in joint session (Joint ACMS-ACCS #27, March 2021)

2.1 Interim decision in relation to nitrous oxide

Proposal

The applicant proposed to create a new Schedule 10 entry for nitrous oxide when supplied in small bulbs, and when not included in Schedule 4 for therapeutic use, to mitigate harms associated with recreational use of the substance.

Interim decision

Pursuant to regulation 42ZCZN of the Regulations, a Delegate of the Secretary has, in relation to the proposed amendment, made an interim decision to amend the scheduling of nitrous oxide in the current Poisons Standard as follows:

Schedule 6 – New Entry

NITROUS OXIDE **except** when included in Schedule 4.

Schedule 4

NITROUS OXIDE for human therapeutic use.

Appendix E, Part 2 – New Entry

POISON	STANDARD STATEMENTS
NITROUS OXIDE when included in Schedule 6.	**A** [For advice, contact a Poisons Information Centre (e.g. phone Australia 13 11 26; New Zealand 0800 764 766) or a doctor.]

Appendix F, Part 1 – New Entry

112. WARNING – May cause irreversible nerve damage if inhaled.

Appendix F, Part 2 – New Entry

38. Do not intentionally inhale contents.

Appendix F, Part 3 – New Entry

POISON	WARNING STATEMENTS	SAFETY DIRECTION
NITROUS OXIDE when included in Schedule 6.	**112** (WARNING – May cause irreversible nerve damage if inhaled.)	**38** (Do not intentionally inhale contents.)

Index – Amend Entry

NITROUS OXIDE

Schedule 6
Schedule 4
Appendix E, Part 2
Appendix F, Part 3

Implementation of labelling requirements

If made final, this change creates new labelling requirements for non-therapeutic nitrous oxide. The statements listed in Appendices E and F would need to be included on both the immediate container and any primary pack, along with requirements set out in Part 2, Section 1 of the Poisons Standard. The required label can be directly printed on, or attached to, the outside of each canister or primary pack; this may include affixing a sticker, provided that it is 'securely attached'.

Part 1 of the Poisons Standard defines "measure packs" as sealed containers, enclosed in a primary pack, that contain a measured quantity of a poison for use on one occasion as a domestic product or pesticide. Part 2, Section 1.5.1 outlines modified labelling requirements for measure packs. The primary pack for these products would remain subject to all labelling requirements for Schedule 6 substances, but each individual canister could use a shorter label as outlined in Part 2 of the Poisons Standard.

Please see Part 2, Section 1 of the Poisons Standard for the full set of labelling requirements and exemptions that apply to Schedule 6 products.

Materials considered

In making this interim decision, the Delegate considered the following material:

- The application to amend the current Poisons Standard with respect to nitrous oxide;
- The 78 public submissions, including 15 written submissions, received in response to the pre-meeting consultation under regulation 42ZCZK of the Regulations;
- The advice received from the meeting of the Advisory Committee on Medicines and Chemicals Scheduling in joint session (Joint ACMS-ACCS #27);
- Subsection 52E(1) of the *Therapeutic Goods Act 1989,* in particular (a) risks and benefits of the use of a substance; (b) the purpose for which a substance is to be used and the and extent of use; (c) the toxicity of a substance; (d) the dosage, formulation, labelling, packaging and presentation of a substance; (e) the potential for abuse of a substance; and (f) any other matters that the Secretary considers necessary to protect public health;
- The Australian Health Ministers' Advisory Council's Scheduling Policy Framework (SPF 2018);
- The Scheduling handbook: Guidance for amending the Poisons Standard;
- A review by Garakani et al., Neurologic, psychiatric, and other medical manifestations of nitrous oxide abuse: A systematic review of the case literature;
- A case report and review by Hathout and El-Saden, Nitrous oxide-induced B_{12} deficiency myelopathy: Perspectives on the clinical biochemistry of vitamin B_{12};

- A letter by Blair et al., Vitamin B_{12} supplementation futile for preventing demyelination in ongoing nitrous oxide misuse;
- A dataset collected by the UK Office for National Statistics; Deaths related to volatile substance abuse and helium, Great Britain; and
- A safety data sheet for compressed nitrous oxide.

Summary of Joint ACMS-ACCS advice to the Delegate

The Committee advised that the current scheduling for nitrous oxide remains appropriate.

Members agreed that the relevant matters under Section 52E(1) of the *Therapeutic Goods Act 1989* included (a) risks and benefits of the use of a substance; (b) the purpose for which a substance is to be used and the and extent of use; (c) the toxicity of a substance; (d) the dosage, formulation, labelling, packaging and presentation of a substance; (e) the potential for abuse of a substance; and (f) any other matters that the Secretary considers necessary to protect public health.

The reasons for the advice included:

a) the risks and benefits of the use of a substance

– Benefits:

§ Benefits in therapeutic use are well established.

§ No benefit of intentional misuse in humans.

§ Widely used as a food additive and there are no other gas replacements that are as suitable.

– Risks:

§ Risk of temporary or permanent haematological or neurological damage with prolonged or high volume inappropriate use.

§ Risk of fatal asphyxiation with high volume use.

§ Low risk at small volumes.

§ Non-toxic when used as a food additive.

b) the purposes for which a substance is to be used and the extent of use of a substance

– Used therapeutically as an analgesic/anaesthetic agent

– Legitimate non-therapeutic uses include; creating whipped cream, mousses and foams; infusing flavours into drinks in the restaurant and catering industry; nitrous oxide injection systems for racing cars; and various scientific applications.

c) the toxicity of a substance

– Low toxicity when small amounts are inhaled for recreational use. Significant toxicity when larger quantities are inhaled for longer periods. The cut-off for increased risk of adverse health outcomes from inhaling large quantities is currently unknown.

– Deactivates vitamin B12, leading to possible neurological and haematological consequences.

– Negligible risk associated with legitimate industrial use (e.g. catering). Therapeutic use is already appropriately regulated and does not require further risk mitigation.

d) the dosage, formulation, labelling, packaging and presentation of a substance

- Most misuse involves the use of small 8 g metal 'bulbs' of nitrous oxide intended for use in cream whipping devices. As these bulbs are not intended for human consumption via inhalation, they do not include any safety labelling.
- There is some evidence of recreational users sourcing larger cylinders intended for use with bulk cream whipping devices. There have also been some reports of medicinal nitrous oxide (Schedule 4) being diverted for recreational use.
- The proposed scheduling risks diverting the misuse of the substance to larger volume canisters. This may lead to increased adverse public health outcomes.

e) the potential for abuse of a substance

- There are increasing reports of misuse, mostly involving low volume intermittent use.
- There is evidence that some recreational users are increasing their typical dosages, and misusing nitrous oxide for longer periods of time, with consequential increased health harms.

f) any other matters that the Secretary considers necessary to protect public health

- Nitrous oxide for non-therapeutic use does not closely fit the scheduling factors for any single schedule. If it were to be scheduled, Schedules 5 or 6 may be the most appropriate category for uses other than inhalation outside a supervised clinical setting (which aligns with Schedule 10).
- States and territories have been implementing their own restrictions.

Reasons for the interim decision (including findings on material questions of fact)

I have decided not to create a Schedule 10 entry for nitrous oxide as proposed by the applicant, though I am of the view that the substance requires scheduling to mitigate its misuse. As such, I have made an interim decision to create a new Schedule 6 entry for nitrous oxide that captures all non-therapeutic uses of the substance. The proposed scheduling also includes the introduction of warning statements, safety labels and safety directions through Appendices E and F of the Poisons Standard. The intention of these labelling requirements is to promote the safe use of products available to the public, and mitigate the harms of their misuse, through educating consumers and suppliers. These changes are not intended to apply to products that are used therapeutically.

I agree with the Committee's findings that the relevant provisions of section 52E of the *Therapeutic Goods Act 1989* are: (a) risks and benefits of the use of a substance; (b) the purpose for which a substance is to be used and the and extent of use; (c) the toxicity of a substance; (d) the dosage, formulation, labelling, packaging and presentation of a substance; (e) the potential for abuse of a substance; and (f) any other matters that the Secretary considers necessary to protect public health.

I note that the applicant proposed to create a Schedule 10 entry for nitrous oxide. However, I agree with the Committee's findings that the substance does not fit the Schedule 10 scheduling factors, outlined in the Scheduling Policy Framework (SPF 2018):

- The risks of nitrous oxide do not substantially outweigh the benefits to the extent that no other Schedule would provide appropriate pubic access.
- While increasing misuse of the substance poses a public health risk, and could warrant tighter controls, these risks do not warrant prohibition.

- Misuse of the substance relates to its potential for abuse and its diversion for illicit use, warranting exclusion from consideration as a Schedule 10 substance.

I note that nitrous oxide is used as an analgesic and anaesthetic agent in medical and dental procedures. It also has several non-therapeutic applications including in hospitality, engineering and scientific research. I agree with the Committee's findings that these uses are significant, difficult to replace, and present negligible risks to the user. I consider that the inclusion of nitrous oxide in Schedule 10, as proposed by the applicant, would unfairly affect legitimate users who can handle the product safely. In light of its substantial benefits and minimal risks when used under normal circumstances, I agree with the Committee's advice that inclusion in Schedule 10 is not appropriate having considered the current body of evidence.

While nitrous oxide does not pose significant risks to users in hospitality (commercial and domestic), engineering and scientific settings, it can produce irreversible toxicity when large volumes are repeatedly and deliberately inhaled in recreational settings. I note the Committee's findings that repeated use can inactivate vitamin B12, resulting in a functional deficiency that can damage the spinal cord and cause permanent disability[1,2]. Worryingly, this deficiency does not appear to respond to supplementation, and is not always picked up in blood tests[3]. The inhalation of nitrous oxide can also displace air, and can act as a fatal asphyxiant. Despite these risks, there have been increasing reports of nitrous oxide abuse in Australia[4], leading to several hospitalisations; deaths are also common in comparable countries such as the UK[5]. These events have been reported predominantly among young individuals who are otherwise healthy. In considering these reports, I have reached the conclusion that nitrous oxide requires further controls that target its misuse.

I disagree with the Committee's advice that the current scheduling of nitrous oxide remains appropriate. In considering further controls, I note that the substance is disproportionately misused when packaged in small, currently unscheduled canisters – commonly known as "nangs". The Committee discussed whether these canisters are classified as food additives by Schedule 14 of the Australia New Zealand Food Standards Code, and would be outside the scope of the Poisons Standard. However, I note that nitrous oxide canisters used in hospitality would fall under the scope of scheduling before their incorporation into food. Moreover, I am of the view that they specifically warrant control through the Poisons Standard, as they present a moderate level of harm, toxicity, health hazard and potential for abuse that clearly relate to scheduling factors listed in the SPF 2018. I further note that the Committee's evaluation of nitrous oxide against the Schedule 6 factors gave a particularly close fit. Having considered the relevant legislation and Committee advice, I have determined that that non-therapeutic nitrous oxide canisters require control through scheduling.

In my view, nitrous oxide fits the Schedule 6 scheduling factors, as outlined in the SPF 2018:

- Nitrous oxide has a moderate to high toxicity if inhaled. Acute inhalation LC_{50} (rat) is between 500 mg/m^3 and 3000 mg/m^3.[6]

- The substance presents a moderate hazard from repeated use, resulting a demonstrable risk of producing irreversible neurotoxicity.

[1] https://doi.org/10.1111/ajad.12372
[2] https://doi.org/10.1016/j.jns.2010.10.033
[3] https://doi.org/10.5694/mja2.50371
[4] https://consultations.health.gov.au/tga/march_2021/user_uploads/quantifying-the-burden-of-n2o-to-emergency-departments-around-wa-v2.2-8-12-20---attachment-1a.pdf
[5] https://www.ons.gov.uk/peoplepopulationandcommunity/birthsdeathsandmarriages/deaths/datasets/deathsrelatedtovolatilesubstanceabuseandheliumgreatbritain
[6] https://www.boc-gas.com.au/en/images/Nitrous%20Oxide%20SDS_tcm351-496573.pdf

- Reasonably foreseeable harm to users can be reduced, to some extent, through strong label warnings. Currently, there are no safety directions, warning statements or first aid instructions for non-therapeutic products containing nitrous oxide.
- The substance has a moderate potential for causing harm.

In determining the scope of a Schedule 6 entry for nitrous oxide, I have considered the committee's findings that that its patterns of misuse may change over time. Since "nangs" are the most widely abused source of nitrous oxide, the initial scheduling proposal targets canisters that fall within a particular size specification. However, I note the Committee's advice that imposing requirements on small canisters, and omitting larger sizes from the same requirements, could divert users or suppliers to larger cylinders. These alternative sources are associated with riskier methods of administration, and increased volumes of administered gas, that may greatly increase the likelihood of asphyxiation. Labelling or restricting access to only small canisters therefore has the potential to drive new use patterns that exacerbate the harms of nitrous oxide abuse.

In making my decision, I have taken into account the 78 public submissions received during the pre-meeting public consultation. I note that 15 submissions included a written component, 6 fully supportive of the applicant's proposal, 5 partially supportive and 4 opposed. Submissions outlined the benefits, harms and proposed regulation from a wide range of perspectives. For example:

- The Royal Perth Hospital Toxicology Service[7] reported a significant increase in nitrous oxide related presentations to emergency departments in Western Australia, and described the use patterns and clinical pathology of these patients. The submission outlined the scope of public health issues relating to nitrous oxide abuse.
- The Australia New Zealand Gas Association[8] outlined both the benefits of nitrous oxide in industry and the dangers of its diversion for misuse. The submission was supportive of introducing stricter controls, noting that there were several possible regulatory approaches.
- The NSW Users and AIDs Association[9] expressed concern that a ban on nitrous oxide may push its use underground and exacerbate any potential harms. The submission emphasised that the adverse impacts of its recreational use are best mitigated through raising awareness, peer education and harm reduction.

On balance, I consider that creating a Schedule 6 entry for nitrous oxide will contribute positively to public health and safety while enabling continued industrial access (hospitality, engineering and scientific research). The new scheduling may directly help mitigate harms through labelling, and complement any educational strategies and counselling associated with substance abuse.

To promote the safe use of nitrous oxide products that are available to the public, I also consider that specific labelling requirements should be mandated through Appendices E and F. Doing so may increase awareness of nitrous oxide-associated neurotoxicity and reduce harms in a significant subset of users. The inclusion of a warning statement that inhalation may cause nerve damage, along with a safety direction to not inhale the substance, may directly help to deter abuse. In those that consume nitrous oxide despite the risks, the inclusion of first aid instructions that refer to a Poisons Information Centre or doctor may assist in early the

[7] https://consultations.health.gov.au/tga/march_2021/user_uploads/quantifying-the-burden-of-n2o-to-emergency-departments-around-wa-v2.2-8-12-20---attachment-1a.pdf
[8] https://consultations.health.gov.au/tga/march_2021/user_uploads/27_01_2021-tga-scheduling-proposal-nitrous-oxide-final_redacted.pdf
[9] https://consultations.health.gov.au/tga/march_2021/user_uploads/nuaa-tga-nitrous-oxide-final-submission-27-01-2021_redacted.pdf

diagnosis and treatment of nerve damage. I am of the view that these labelling requirements may help alert users of potential harms.

I have carefully considered the feasibility of labelling nitrous oxide products with these statements, given the wide variety of pack sizes and presentations. I note that Part 2 of the Poisons Standard requires that both primary packs and immediate containers of scheduled poisons are labelled; for large cylinders, I am of the view that this would not present any significant barrier to legitimate manufacture, sale or use of nitrous oxide. I further note that primary packs of small canisters may be captured by the definition for "measure pack" given in Part 1 of the Poisons Standard, and would therefore be eligible for simplified labelling requirements specified in Part 2, Section 1.5.1. I am of the view that these existing provisions appropriately mitigate the impact on industry, while maintaining the public health benefits of labelling.

In making my decision, I note that the regulation of nitrous oxide is not solely a scheduling issue. I consider that raising awareness amongst young people about the risks, especially the potential for permanent nerve damage, is an important step to reducing hospitalisations and deaths – and that labelling is only one mechanism towards achieving this goal. I note that various States and Territories are also implementing their own strategies and restrictions for mitigating the risk from the inappropriate use of nitrous oxide. I am of the view that creating a Schedule 6 entry for nitrous oxide will support these ongoing efforts.

I have therefore made an interim decision to create a Schedule 6 entry for non-therapeutic nitrous oxide, along with accompanying label statements set out in Appendices E and F. I am of the view that these changes will help mitigate the harms associated with abuse of the substance, especially the potential for permanent nerve damage.

Due to the widespread presence of nitrous oxide in many different products, I have decided on a later implementation date of 1 October 2022. This should allow sufficient time for industry to make the necessary changes to respond to the new labelling requirements.

Proposed implementation date

1 October 2022