Medicines & Healthcare products
Regulatory Agency

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[redacted]

04 October 2023

Dear [redacted]

FOI 23/660 - Nitrous oxide.

Thank you for your email of 7 September 2023 regarding the medical and social use of nitrous oxide. More specifically, you asked whether we were aware of any recent medical studies suggesting carcinogenic qualities of the gas.

> *"I am looking for further information and any recent medical studies that you might be aware of on the medical and social use of nitrous oxide (laughing gas/entonox), under the Freedom of Information Act.*
>
> *With the laughing gas ban and 'increased hospital admissions' alongside the query over reducing the usage of Entonox for labouring mothers, I am curious as to whether there have been any recent studies which have suggested carcinogenic qualities of the gas that we were previously unaware of.*
>
> *If you cannot help directly, please point me in the direction of someone who can."*

In the UK, there are currently 7 licences for medical nitrous oxide, held by 4 market authorisation holders as summarised the table below. Nitrous oxide is authorised as a weak anaesthetic and an analgesic.

These are provided in the following table:

Authorisation Number	Product Name	Legal Status Type	Authorisation Holder Company Name
PL 00735/5001R	BRITISH OXYGEN MEDICAL NITROUS OXIDE	P	BOC LIMITED
PL 00735/5017R	ENTONOX MEDICINAL GAS	P	BOC LIMITED
PL 15929/0004	AIR LIQUIDE MEDICAL NITROUS OXIDE	P	AIR LIQUIDE LIMITED
PL 15929/0008	EQUANOX	P	AIR LIQUIDE LIMITED
PL 17872/0001	NITRONOX INHALATION GAS	P	MEDICAL GAS SOLUTIONS LIMITED
PL 35326/0009	DONOPA MEDICINAL GAS, COMPRESSED 50%/50% V/V	POM	SOL SPA
PL 35326/0010	SOL NITROUS OXIDE MEDICINAL GAS100% V/V	POM	SOL SPA

The legal status determines its availability, either under the supervision of a pharmacists (P) or by prescription only (POM). Product information for the above licences is available from the MHRA website at: MHRA Products | Search results. Please note that some of these results will highlight other medicines which may have an interaction with nitrous oxide.

For the part of your request asking for any recent medical studies, under section 1(1)(a) of the FOIA, we do not hold this information. We are not aware of any ongoing medical studies regarding carcinogenic qualities of the gas, and no new safety concerns have been identified with nitrous oxide with respect to this. As with all medicines and medical devices, we continuously monitor the safety of nitrous oxide and would inform healthcare professionals and the public if there was any important new safety information.

The total number of Yellow Card reports that we have received concerning adverse reactions to medicines containing nitrous oxide is available on the MHRA interactive Drug Analysis Profile. We can confirm that as of 31 August 2024 we have not received any Yellow Card reports under the Neoplasms benign, malignant and unspecified (incl cysts and polyps) System Organ Class.

The total number of reactions reported to the Yellow Card database have increased over the past 10 years. Prior to 2013, total numbers of reactions reported were low. The number of reactions reported for 2023 are up to 31 August 2023. However, it is important to note that there can be a number of factors that impact the reporting of Yellow Cards and conclusions cannot be extrapolated from reporting frequencies.

In the past 10 years we have received:

Year Received	Non-Serious	Serious (excluding fatal)	Fatal	Total
2013	0	4	0	4
2014	0	13	0	13
2015	1	12	1	14
2016	1	7	0	8
2017	2	14	0	16

2018	1	10	0	11
2019	1	14	1	16
2020	1	5	0	6
2021	1	5	0	6
2022	4	13	0	17
2023	6	19	0	25
Total over last 10 years	**18**	**116**	**2**	**136**
Total since first received report	**29**	**177**	**16**	**222**

It also should be noted that this is a voluntary scheme, therefore there may be under-reporting especially with this well-known gas. When using the Interactive Drug Analysis Profile, you should remember that:

- The likelihood of experiencing an adverse drug reaction when taking a medicine cannot be estimated from the data in the Interactive Drug Analysis Profile. This is because we have limited information about how many people have taken the medicine without experiencing a reaction.
- Reporters are asked to submit Yellow Card reports even if they only have a suspicion that the medicine may have caused the adverse drug reaction. The existence of an adverse drug reaction report in the Interactive Drug Analysis Profile does not necessarily mean that the medicine has caused the reaction.
- It may be difficult to tell the difference between something that has occurred naturally and an adverse drug reaction. Sometimes reactions can be part of the condition being treated rather than being caused by a medicine.
- Many factors have to be considered when assessing whether a medicine has caused a reported adverse drug reaction. When monitoring the safety of medicines, MHRA staff carry out careful analysis of these factors.
- It is not possible to compare the safety of different medicines by comparing the numbers presented in the Interactive Drug Analysis Profiles. Reporting rates can be influenced by many factors including the seriousness of the adverse drug reactions, their ease of recognition and the extent of use of a particular product. Reporting can also be stimulated by promotion and publicity about a product.

Nitrous oxide is also reviewed regularly through a European periodic safety update report single assessment (PSUSA) by the Pharmacovigilance Risk Assessment Committee (PRAC) and the Heads of Medicines Agencies (CMDh) at the European Medicines Agency. The CMDh publish their decisions should a recommendation be made to update the product information. There have not been any updates that highlight carcinogenic effects. The decisions may be found at: Medicines | European Medicines Agency (europa.eu)

Nitrous oxide is also used non-medically in the food industry, agriculture and others. However, we are aware of the safety concern of abuse. In June 2023, the government decided to control nitrous oxide under the Misuse of Drugs Act 1971 as a class C drug. The Advisory Council on the Misuse of Drugs (ACMD) proposed the classification of nitrous oxide under the Misuse of Drugs Regulations 2001 owing to increased misuse. The makes provision for the continued use of nitrous oxide for legitimate reasons.
Advice on scheduling and lawful access to nitrous oxide - GOV.UK (www.gov.uk)

We hope that this information has been useful to you.

Appeal rights

If you have a query about this email, please contact us.

If you are unhappy with our handling of your request, you may ask for and internal review.

After a review, if you remain dissatisfied, you may ask the Information Commissioner for a decision at:

The Information Commissioner's Office
Wycliffe House
Water Lane
Wilmslow
Cheshire
SK9 5AF

Yours sincerely,

Safety & Surveillance
MHRA