**The environmental impact of commonly used anaesthetic agents: a systematic literature review and qualitative evidence synthesis protocol**

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Introduction

The scientific evidence for warming of the climate system is now unequivocal and the prevention of further global warming now represents mankind’s biggest challenge. The rate of global warming over the past 150 years is now happening at a faster rate than in preceding millennia. The United Nations Framework Convention on climate change (UNFCCC) has set a goal of holding the increase in global average temperature to less than 1.5 oC above pre-industrial levels. Green-house gas (GHG) emissions urgently need to be reduced if this goal is to be achieved.[1][2] International treaties such as the Kyoto Agreement and the Montreal Protocol have resulted in a near universal commitment from nations around the world to reduce the release of green-house gases and substances that act to deplete the ozone layer.[3][4]

Volatile inhalational anaesthetic agents are halogenated fluorocarbons which have greenhouse warming potential (GWP). They are now detectable even in the atmosphere in the arctic at significant levels.[5] Each year, more than 310 million anaesthetics are given worldwide and operating theatres are an appreciable source of greenhouse gas emissions.[6][7] Volatile inhalational anaesthetic agents are little changed by human metabolism and excreted through the lungs. In modern operating theatres, they are scavenged from the circulating room air and eliminated directly into the atmosphere. However, whilst the ozone depletion potential from halogenated green-house gases such as Desflurane, Sevoflurane and Isoflurane is evident, actual estimates of such an effect are purely speculative.

The relative environmental merits of alternative anaesthetic techniques remains uncertain. These merits may be classified according to the “cradle to grave” analysis of drugs used, and can include the environmental impact of the plastic packaging, methods of disposal and transport of components required to manufacture the drug. The production and entire lifecycle of sterile intravenous agents also has a climate impact and may also represent a significant carbon footprint.[8] Nevertheless, with increasing awareness of the potential environmental impact of anaesthetic volatile drugs, calls for a reduction in their use and the use of alternative intravenous anaesthetic agents, especially propofol, are increasingly made in a bid to reduce the anthropogenic effects of anaesthesia [9] . Any change in anaesthetic practice must be informed and based upon science rather than opinion if unintended anthropogenic consequences are to be avoided. Without such evidence, it will also be impossible to weigh the environmental merits of any given anaesthetic technique against outcomes for individual patients. We will perform a systematic review and evidence synthesis to establish the current knowledge on this important topic. We aim to describe the existing evidence and compare the environmental impact of commonly used, atmospherically detectable volatile anaesthetic agents with that of intravenous anaesthetic drugs.

Review question / Problem/domain to be studied

What is the anthropogenic impact of anaesthetic drugs, as defined by the World Health Organisation essential medicines checklist of anaesthetic drugs? Specifically, we will focus on intravenous anaesthetic drugs, muscle relaxants, local anaesthetic agents and volatile anaesthetic agents.

We have used the list of anaesthetic agents as defined in the World Health Organisation essential drugs list in sections to define those to be included in this review:

1.1.1 (volatile anaesthetic agents): Halothane, Isoflurane, Nitrous Oxide

1.1.2 (IV anaesthetic agents): Propofol, Ketamine, Thiopentone

1.2 (Local anaesthetic agents): Bupivicaine, Lidocaine

20 (Muscle relaxants): Atracurium, Suxamethonium, Vecuronium, Neostigmine

We will also include the commonly used inhalational agents of interest: Sevoflurane, Desflurane

Oxygen will be excluded from 1.1.1 as we anticipate a vast number of records that are not specific to anaesthesia.[10]

We aim to describe the existing evidence regarding the environmental impact of anaesthetic drugs listed on the WHO essential medicines list.[10] This review will include the following anaesthetic drugs: volatile anaesthetic agents; Halothane, Isoflurane, Nitrous Oxide and the intravenous anaesthetic agents Propofol, Thiopentone and Ketamine. It will also include the muscle relaxants, atracurium, suxamethonium and vecuronium and the local anaesthetic drugs lidocaine and bupivacaine. Additionally, we will include the volatile agents sevoflurane and desflurane with the rationale that they are detectable in the atmosphere (as defined by the SOGE programme) and ecosystem. [11]

Intervention/exposure

The review will include an assessment of the global environmental impact, and potential for environmental harm, of the anaesthetic drugs listed above. We will include the contribution to the greenhouse warming effect of each drug (that is their greenhouse warming potential, GWP), indirect emissions effect, and lifecycle analysis (impact of their manufacture, transport, disposal) data where available for each drug.

Comparator/control

We will compare the differential impacts of the anaesthetic agents where possible.

Main outcome

We will define what literature is available about the environmental impact of the whole life cycle of the anaesthetic drugs as defined by the world health organisation essential medicine list (sections: 1.1.1, 1.1.2, 1.2, 20) and two inhalational agents central to the environmental impact debate in anaesthesia (sevoflurane and desflurane).

We will describe the overall climate fingerprint, including the greenhouse gas effect, ozone depletion potentials, manufacture/production/disposal and carbon footprint of each drug. Where information on the full life cycle of an agent is available, this will be presented.

We will use the following methodology in our review but anticipate this will be an iterative process.

Searches

We developed our search strategy based on an adapted PICO format and upon a combination of terms referring to anaesthetic agents listed above and terms associated with environmental impact.

We will search MEDLINE (PudMed), Excerpta Medica dataBASE (EMBASE), Cumulative index to nursing and allied health literature (CINAHL) using the Health Database Advanced Search platform from inception until 09/10/2019.

Additional searches for these specific agents will be performed on DrugBank (<https://www.drubank.ca/>) to obtain any relevant information regarding their environmental impact.

We will include any scientific study that sheds light on the anthropogenic effect of the aforementioned drugs and any studies in any population (including animal or human) where the study reports the environmental impact of aforementioned anaesthetic agents.

Data extraction will include any domain specific terms relevant for an environmental impact (for example specialist terms relating to climate change) and searches will be re-run for these terms and listed anaesthetic agents to ensure comprehensive capture of environmental impacts.

Search terms

#inhalationals

(sevoflurane).ti, ab OR (desflurane).ti, ab OR (isoflurane).ti, ab OR (halothane).ti, ab OR (nitrous).ti, ab OR (nitrous oxide).ti, ab

#IV

(ketamine).ti, ab OR (propofol).ti, ab OR (thiopentone).ti, ab OR (thiopental).ti, ab

#Muscle

(succinylcholine).ti, ab OR (suxamethonium).ti, ab OR (vecuronium).ti, ab OR (atracurium).ti, ab OR (neostigmine).ti, ab OR (pyridostigmine).ti, ab

#LA

(bupivicaine).ti, ab OR (lidocaine).ti, ab OR (lignocaine).ti, ab

#outcomes

(environmen\*).ti, ab OR (pollut\*).ti, ab OR (waste\*).ti, ab OR (greenhouse).ti, ab OR (ozone).ti, ab OR (contaminat\*).ti, ab OR (ecolog\*).ti, ab OR (carbon).ti, ab OR (warming).ti, ab OR (climate).ti, ab

Types of study to be included

Basic Science, physical chemistry, laboratory research papers

Clinical studies

Human, Animal studies

All languages

Studies will be included if they include the drugs as defined by the WHO medicines list for anaesthesia:

1.1.1 (volatile anaesthetic agents): Halothane, Isoflurane, Nitrous Oxide

1.1.2 (IV anaesthetic agents): Propofol, Ketamine, Thiopentone

1.2 (Local anaesthetic agents): Bupivicaine, Lidocaine

20 (Muscle relaxants): Atracurium, Suxamethonium, Vecuronium, Neostigmine

OR

commonly used inhalational agents of interest: Sevoflurane, Desflurane

Studies will be selected if they include data on any part of the 'cradle to grave' life cycle of the drugs which will be classified as one of seven steps:

1. Raw materials (where do they come from, how are they sourced)

2.Manufacturing process of the agent: to include but not be limited by - energy used, solvents used, isolation/purification procedure what happens to the waste of manufacture

3.Packaging - making the packaging (glass ampules/metal cannisters/boxes/plastic)

4. Distribution, transport and delivery of drug product

5. Disposal (methods of) of waste packaging, including needles, syringes, infusion sets etc.

6. Disposal of expired drug

7. Excretion of drug and metabolites from the patient - for example - water waste treatment/scavenging

Any study presenting research data will be included, studies will be excluded if they present expert opinion only.

Screening and selection of papers

Records will be held in a dedicated Mendeley group. Duplicates will be removed. The title and abstract of each record will be screened in duplicate by investigators acting independently against the following criteria;

Type of study: all studies except for expert opinion

Inclusion of the specific drugs as described in population/inclusion criteria: Propofol, ketamine, midazolam, halothane, sevoflurane, isoflurane, desflurane, nitrous oxide, Atracurium, Suxamethonium, Vecuronium, Neostigmine, Bupivicaine, Lignocaine

Reporting of any environmental impact assessment and/or life cycle analysis: global warming potential, atmospheric life time, indirect and direct carbon dioxide emissions, effect on soil/water/ecosystem from point of manufacture through to disposal.

After screening, the full text of any record selected for inclusion by any investigator will be obtained. Full texts will then be assessed by two independent reviewers against the above inclusion criteria. Any discrepancies between reviewers will be adjudicated by a third member of the team. The reason for exclusion of studies excluded at this stage will be documented. The references will be screened for each paper for other relevant papers to be included.

Data extraction from full texts

Data collected will be in the following domains for all papers:

1. Article information

- Title of the article

- Drug investigated and reported upon

- Lead Author

- Year of publication

- Year of study completion

2. Study characteristics

- Geographical location of centres

- Type of paper and methodology of study

We will create a drop down table for each of the life cycle analysis which will be classified in the following domains:

1. Raw materials: where do they come from, how are they sourced.
2. The manufacturing process of the agent: to include but not be limited by - energy used, solvents used, isolation/purification procedure what happens to the waste of manufacture
3. Packaging  - making the packaging (glass ampules/metal cannisters/boxes/plastic)
4. Distribution, transport and delivery of drug product
5. Disposal (methods of) of waste packaging, including needles, syringes,
6. Disposal of expired drug
7. Excretion of drug and metabolites from the patient - water waste treatment/scavenging

If we identify drugs with sufficient information available to describe a full cradle-grave life-cycle analysis, then we will perform this. This will include information about the raw materials required to produce the drug or packaging, how it may be disposed of, the transportation and storage of a product and how it is disposed of into the ecosystem. If this is the case, then the protocol will be updated to include a statistical analysis plan of how these data will be synthesised. We anticipate this will be an iterative process.

Data extraction will take place with piloted, standardised, web based data extraction form. (GoogleForm, Google, Alphabet Inc), which will automatically populate a spread sheet (GoogleSheet, Google, Alphabet Inc). Data extraction and inclusion steps will be performed in duplicate.

Risk of bias (quality) assessment

We will include papers in all languages and arrange for translation as required. Risk of bias in included studies will be determined using tools appropriate for the study design. The Cochrane Risk of Bias Tool, version 2 (ROBT2) will be used for Randomised Trials, the Newcastle Ottawa scale will be used for observational studies. Where other designs are identified we will use tools as recommended within the [Cochrane Handbook](https://training.cochrane.org/handbook) We will not exclude studies at high risk of bias, and will present standardised risk of bias tables.

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