PEER REVIEW HISTORY

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ARTICLE DETAILS

TITLE (PROVISIONAL)	The environmental footprint of morphine; a life cycle assessment from opium poppy farming to the packaged drug.
AUTHORS	McAlister, Scott; Ou, Yanjun; Neff, Elise; Hapgood, Karen; Story, David; Mealey, Philip; McGain, Forbes

VERSION 1 - REVIEW

REVIEWER	Hugh Montgomery University College London, UK I have an active interest in Climate Change and Health. I am, for instance, a member of the UK Climate and Health Council. I have worked on two 'Lancet Commissions' on Climate Change and Health. These roles are unpaid.
REVIEW RETURNED	17-Jul-2016

GENERAL COMMENTS	I enjoyed reading this study, which is well presented and free, to my eye, of major flaws. My sole comments are minor: Introduction: LCA has been used to estimate healthcare's entire 'carbon footprint' for nation states, and has been found to be responsible for 8% of the 2009 United States' CO2 emissions. Introduction: 'Major factors influencing a drug's environmental footprint are; ' The semicolon is superfluous. Introduction: 'that doctors' prescribe, ' The apostrophe should be removed. Introduction: A brief explanation of CO2 equivalent emissions (CO2 e) might help those unfamiliar with the concept. Methods: 'despite repeated requests from the manufacturers' should read 'despite repeated requests to the manufacturers.' Table 1, point 6: 'resulting in dried cakes.' The fullstop doesn't appear at the end of other lines in the table. Methods: 'Raw Material Spreadsheet', that records..' The comma is extraneous. Methods: 'The morphine production step, however is not connected to the Energy Matrix, thus we calculated associated electricity use by..' Should read, 'The morphine production step, however is not connected to the Energy Matrix. We thus calculated...' OR 'Because the morphine production step is not connected to the Energy Matrix,

	we calculated associated electricity use by..' Methods: 'Packaging for 100mg morphine required; 16 g PVC as the enclosing plastic bag, 9 g HDPE plastic as the overwrapping pouch, and 9 g cardboard box required for each ...' The second 'required' should be removed. The semicolon isn't needed. Methods: 'The following impact categories (and their units) were calculated: climate change, (g CO2 equivalents), ozone depletion, (kg trichorlfluoromethane (CFC-11) equivalents), photochemical oxidant (smog) formation, (kg non-methane volatile organic compound (NMVOC) equivalents), and human, terrestrial and marine ecotoxicity, (kg 1,4- dichlorobenzene (1,4-DB) equivalents).' This might be better as, 'The following impact categories (and their units) were calculated: climate change (g CO2 equivalents), ozone depletion (kg trichorlfluoromethane (CFC-11) equivalents), photochemical oxidant (smog) formation (kg non-methane volatile organic compound (NMVOC) equivalents), and human, terrestrial and marine ecotoxicity (kg 1,4- dichlorobenzene (1,4-DB) equivalents).' Results: 'morphine sulphate from;..' The semicolon isn't needed. Results: 'than 100mg of morphine(Table 2).' A space is needed between 'morphine' and 'Table 2)' Results: 'Ozone depletion arose predominately arising from farming.' The word 'arising' should be removed. Results: Table 2 title: 'assessment for;' The semicolon can be removed. Results: 'required; 16 g' The semicolon isn't needed. Discussion: 'Morphine's environmental effects were small for climate change (204g CO2 eq), and very small for all other effects examined.' It should be made clear that this relates to 100mg morphine e.g. 'The environmental effect of producing 100mg morphine was small for climate change (204g CO2 eq)..' OR 'Morphine's environmental effects were small for climate change (204g CO2 eq per 100mg manufactured drug), and ...' Discussion: The introduction states that 'the UK National Health Service (NHS) contributed more than 20% of the total CO2 emission....' The discussion states that '..approximately 20% of the entire carbon footprint of England's National Health Service was due to drug production and use. ' Is the 20% figure this for English NHS, or whole UK NHS (England +Scotland +Wales +N Ireland)? Likewise 'The UK England purchase costs for morphine as a proportion of the total English..' Which? UK or England? This sentence could be clarified.. Normalisation has been correctly performed using the average Australian's data (18.3 tonnes of CO2 per annum) given that the LCA. Was performed in Australia. However, Australia is a big emitter per capita when compared to many other countries, and this 'normalisation' has the effect of diminishing the perceived scale of emissions. UK emissions (2011) were a little over 7 tonnes/capita,

	and Finland a little over 10 tonnes/capita. By such comparison, the CO2 cost is actually quite high. Further, 1kg CO2 is a=circa 559 litres at 27oC and standard atmospheric pressure. So 100mg morphine is responsible for 114 litres CO2: in other words, 1g morphine is responsible for about 1litre of CO2. That's a lot- and such scaling might be worth mentioning.

REVIEWER	Jerome Baddley The Sustainable Development Unit for the Health and Social Care System England No directly competing interests. However, advice and guidance was sought on the research from 2 members of Unit staff prior to my joining the Unit. Their names, Tom Penny and Imogen Tennison are listed in the acknowledgements.
REVIEW RETURNED	22-Jul-2016

GENERAL COMMENTS	This is excellent and well considered work that contributes to the emerging knowledge base on the environmental impacts of pharmaceuticals. The Unit look forward to seeing further work in this area to confirm the authors assertion in the discussion (pg 15 lines 28-32) that "Even if morphine's environmental footprint was exceptionally low compared to other pharmaceuticals, the final drug production stages and packaging are likely to have the largest environmental effects for most drugs". Disposal and use were quite reasonably set as outside of the boundaries of this work. Given this studies discovery of the apparent importance of packaging and final production stages, in future studies it would be valuable to see these included for comparison with the impact of earlier production stages. It would seem that packaging and possibly unused product disposal may form a significant proportion of the lifecycle impact. Packaging design and final production stages are designed particularly to support distribution and use. With future studies with other products, it would also be interesting to see the relative impacts allocated to distribution, storage, use and disposal, where packaging and final production stages may have an even more pronounced downstream impact, such as temperature sensitive products or products whose chosen delivery mechanisms result in fugitive GHG emissions in use and disposal.

REVIEWER	Jodi Sherman Yale University, School of Medicine, Department of Anesthesiology
REVIEW RETURNED	03-Aug-2016

GENERAL COMMENTS	General Comments: • The article addresses an important and novel topic to health care and global health, the climate emissions that stem from pharmaceutical drugs using morphine as a key example. The authors do a reasonable job of making this case, though need to improve upon their justification/methods for their focus on Australia. Are there only two manufacturers in Australia that supply 50% of the global licit supply? Are they the only suppliers for Australia? Where

	are the other suppliers? • The single greatest obstacle to understanding the environmental emissions of pharmaceuticals (and also devices) is the proprietary nature of synthesis. Standard portions of the manufacturing process, namely the active pharmaceutical ingredient, have been published. However, how ingredients are put together is confidential. Industry publications of their LCAs therefore cannot be verified, which is a weakness and primary justification for the study. The authors need to do a better job of spelling this out clearly for the readers. In fact, this should be the entire frame of their paper. • The paper would be more readable if methods and results were broken down by subheadings for the respective stages: farming, extraction, preparation. • There is virtually no discussion of non-CO2 emissions, and the paper would be much clearer if it stayed focused on just the CO2 emissions and the remaining emissions are moved to a supplemental section. • The authors struggle to contextualize their findings. While there is good national data on licit opioid requirements, the proportional breakdown of the types of formulations is never made clear. They rightfully try to compare their findings to the UK, but do so in a convoluted way with only a modest caution. They look at expenditures from the UK SDU on morphine to come up with a percentage of daily UK citizen CO2 contribution, and compare to their process results and findings of daily Australian citizen CO2 contribution, to say they are similar and therefore their results are a little verified. This metric makes no sense. Instead they ought to derive the weight-based emissions from the UK SDU economic method and compare that to their findings. • The final life stage of the 100mg/100ml morphine manufacturing--preparation and packaging--is significant, so it shouldn't be left out. They do some hand waving about how other preparations are likely comparable, and multiply by Australian national Yet they only have data from one type of formulation 100mg MSO4/100ml NS. They mix multiple methods to justify the reasonableness of their extrapolation. The method here is convoluted. Maybe, if they could clarify this more it might fly. • This is not a pure process LCA, e.g., the authors use economic input-output for part of their analysis of GSK processes in order to attribute emissions between poppy extracted pellets and seeds. Later on, (in the discussion where it's location is suspect) they include results on analysis of glass ampoule packaging. They bring in a bit of their own process study of the glass ampoule packaging in the discussion section (?!) when they could just use it in the body of their paper and call this a hybrid LCA (which it already is.) Comments by Section: Strenths/weaknesses • Remove statements in Strengths (and also Conclusion section) "… one of the the very few….", or "….the only…", or similar type statements. • The methods for extrapolation to Australian national estimation are problematic, and may need to be removed if they can't be fixed • The very last point reads in a very confusing manner. In fact, that the authors worked with industry could be turned into a paper strength. Abstract • This is not 'cradle-to-grave' in that it is limited to manufacturing, even if authors were to call it such within the systems boundary of

	manufacturing. There appears to be no overt accounting of use/reuse (e.g. solvents) or waste management, and so it's hard to even call it 'cradle-to-gate'. Authors need to be more clear on use/reuse and waste phases to call it the latter. • This is not entirely process based, e.g. the authors use economic surrogate data for GSK pelletizing and poppy seed extraction. It is therefore appropriate to call this a hybrid LCA. • The vast majority of the paper focuses on CO2e, and thus this ought to be named the primary outcome measure. All others are secondary, and indeed only given cursory space. The authors should strongly consider leaving out the secondary measures completely, or relegating them to the supplemental material as they do not appear to add anything to the paper and distract from the topic at hand. • It is unclear that the author's achieved sufficient rigor to characterize their results in terms of an Australian's daily CO2 emissions. While important to contextualize, this stretch may not be possible. Introduction • There is a more recent reference of the US healthcare footprint you should use, Eckelman in PONE. • It is incorrect to state that the UK NHS SDU has developed a protocol to perform pharmaceutical LCAs. (IF they have, then what is it?) IT is correct to say that they have called for it. • IF you are going to focus attention to Australian formularies, then you need to say something about the size of the Australian health sector. IF the carbon footprint is unknown, say so. At the very least you can describe the size in terms of national health care costs and percent of GDP, so we can begin to understand some comparatives between the US and the UK. • Please explain what an alkaloid is. How is this different from raw extracts? • Why are you aiming to quantify morphine's environmental effects? It is left un/understated why you are interested in CO2, water use, aquatic and terrestrial pollution. • You move from Australia production of 50% of global alkaloids exported, to looking at Australian common preparations (ampoule and bag). You need to transition to/say more about the Australian health market if you want to focus on Australian preparations. • What is GSK and why did you enter in a study with them and Baxter? Methods/Results: See general comments above Discussion • You introduce new methods and results here, namely the breakdown of the glass ampoule. Unless this is published, then it belongs either in the methods section or ought to be left out (see general comments above.)

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1
Reviewer Name

Hugh Montgomery

Institution and Country

University College London, UK

Please state any competing interests or state ‘None declared’:
I have an active interest in Climate Change and Health. I am, for instance, a member of the UK Climate and Health Council. I have worked on two 'Lancet Commissions' on Climate Change and Health. These roles are unpaid.

Please leave your comments for the authors below.

I enjoyed reading this study, which is well presented and free, to my eye, of major flaws.
We thank Reviewer 1 (Prof. Montgomery) for his encouraging words.

My sole comments are minor:
Introduction: LCA has been used to estimate healthcare’s entire ‘carbon footprint’ for nation states, and has been found to be responsible for 8% of the 2009 United States’ CO2 emissions.
Amended as suggested by Reviewer #1.

Introduction: ‘Major factors influencing a drug’s environmental footprint are; ‘ The semicolon is superfluous.
Amended as suggested by Reviewer #1.

Introduction: ‘that doctors’ prescribe, ‘ The apostrophe should be removed.
Amended as suggested by Reviewer #1.

Introduction: A brief explanation of CO2 equivalent emissions (CO2 e) might help those unfamiliar with the concept.
Page 5, paragraph 1, Introduction. Amended as suggested by Reviewer #1.
“Kg CO2eq is the standard unit for measuring carbon footprints and expresses the global warming potential of different greenhouse gas in “CO2 equivalents” that would create the same amount of warming.27”

Methods: ‘despite repeated requests from the manufacturers’ should read ‘despite repeated requests to the manufacturers.’
Amended as suggested by Reviewer #1.

Table 1, point 6: ‘resulting in dried cakes.’ The fullstop doesn’t appear at the end of other lines in the table.
Amended as suggested by Reviewer #1.

Methods: ‘Raw Material Spreadsheet’, that records..’ The comma is extraneous.
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Amended as suggested by Reviewer #1.

Methods: ‘Packaging for 100mg morphine required; 16 g PVC as the enclosing plastic bag, 9 g HDPE plastic as the overwrapping pouch, and 9 g cardboard box required for each ...’ The second ‘required’ should be removed. The semicolon isn’t needed.
Amended as suggested by Reviewer #1.

Methods: ‘The following impact categories (and their units) were calculated: climate change, (g CO2 equivalents), ozone depletion, (kg trichorlfluoromethane (CFC-11) equivalents), photochemical oxidant (smog) formation, (kg non-methane volatile organic compound (NMVOC) equivalents), and human, terrestrial and marine ecotoxicity, (kg 1,4- dichlorobenzene (1,4-DB) equivalents).’ This might be better as, ‘The following impact categories (and their units) were calculated: climate change (g CO2 equivalents), ozone depletion (kg trichorlfluoromethane (CFC-11) equivalents), photochemical oxidant (smog) formation (kg non-methane volatile organic compound (NMVOC) equivalents), and human, terrestrial and marine ecotoxicity (kg 1,4- dichlorobenzene (1,4-DB) equivalents).’
Amended as suggested by Reviewer #1.

Results: ‘morphine sulphate from;..’ The semicolon isn’t needed.
Amended as suggested by Reviewer #1.

Results: ‘than 100mg of morphine(Table 2).’ A space is needed between ‘morphine’ and ‘Table 2)’
Amended as suggested by Reviewer #1.

Results: ‘Ozone depletion arose predominately arising from farming.’ The word ‘arising’ should be removed.
Amended as suggested by Reviewer #1.

Results: Table 2 title: ‘assessment for;’ The semicolon can be removed.
Amended as suggested by Reviewer #1.

Results: ‘required; 16 g’ The semicolon isn’t needed.
Amended as suggested by Reviewer #1.

Discussion: ‘Morphine’s environmental effects were small for climate change (204g CO2 eq), and very small for all other effects examined.’ It should be made clear that this relates to 100mg morphine e.g. ‘The environmental effect of producing 100mg morphine was small for climate change (204g CO2 eq)..’ OR ‘Morphine’s environmental effects were small for climate change (204g CO2 eq per 100mg

manufactured drug), and ...'
Amended as suggested by Reviewer #1.

Discussion: The introduction states that 'the UK National Health Service (NHS) contributed more than 20% of the total CO2 emission....' The discussion states that '..approximately 20% of the entire carbon footprint of England's National Health Service was due to drug production and use. ' Is the 20% figure this for English NHS, or whole UK NHS (England +Scotland +Wales +N Ireland)? Likewise 'The UK England purchase costs for morphine as a proportion of the total English..' Which? UK or England? This sentence could be clarified..
Thank you for noting this inconsistency: the 20% figure is for England's NHS (not the UK's). The morphine costs though are correct, i.e. for England only (Ref. 35).
Page 4, paragraph 1, Introduction.
"In 2012 the production of all pharmaceuticals used by England's National Health Service (NHS) contributed more than 20% of the total CO2 emissions (i.e. all purchasing, energy use and transport) arising from the NHS's activities.4"

Normalisation has been correctly performed using the average Australian's data (18.3 tonnes of CO2 per annum) given that the LCA. Was performed in Australia. However, Australia is a big emitter per capita when compared to many other countries, and this 'normalisation' has the effect of diminishing the perceived scale of emissions. UK emissions (2011) were a little over 7 tonnes/capita, and Finland a little over 10 tonnes/capita. By such comparison, the CO2 cost is actually quite high. Further, 1kg CO2 is a=circa 559 litres at 27oC and standard atmospheric pressure. So 100mg morphine is responsible for 114 litres CO2: in other words, 1g morphine is responsible for about 1litre of CO2. That's a lot- and such scaling might be worth mentioning.
We provide further explanation about the role of normalization in the Methods.
Page 9, paragraph 2, Methods.
"Normalisation is a method used to indicate the relative importance of an impact category; we 'normalised' the results for each impact category (i.e. divided our results by an average Australian's per capita emissions in each category) as per ISO 14044.28 Normalisation takes into account potential effects from national electricity and fuel mixes. Per capita, Australia is a high emitter of CO2e which may appear to reduce the environmental impacts of morphine production. Nevertheless, morphine made in the UK, for example, would have a lesser climate change impact (CO2e) than morphine made in Australia due to the different electricity mix. A lesser environmental impact being compared to a lesser per capita emission may be comparable to the normalisation percentage of Australia."

Reviewer #1 asks that we consider mentioning the effects of morphine production in terms of litres of CO2. Whilst we agree that this would be potentially useful to indicate the scale of the CO2 effects of morphine production it is routine in life cycle assessment to use kg as the unit for CO2, not litres as suggested.

Reviewer: 2

Reviewer Name: Jerome Baddley

Institution and Country: The Sustainable Development Unit for the Health and Social Care System, England

Please state any competing interests or state 'None declared':
No directly competing interests. However, advice and guidance was sought on the research from 2

members of Unit staff prior to my joining the Unit. Their names, Tom Penny and Imogen Tennison are listed in the acknowledgements.

Please leave your comments for the authors below
This is excellent and well considered work that contributes to the emerging knowledge base on the environmental impacts of pharmaceuticals. The Unit look forward to seeing further work in this area to confirm the authors assertion in the discussion (pg 15 lines 28-32) that "Even if morphine's environmental footprint was exceptionally low compared to other pharmaceuticals, the final drug production stages and packaging are likely to have the largest environmental effects for most drugs".

We thank Reviewer #2 (Jerome Baddley) for his kind and encouraging words. We agree that further work in this area is most certainly needed and that analyses of the life cycles of drugs is at a nascent state.

Disposal and use were quite reasonably set as outside of the boundaries of this work. Given this studies discovery of the apparent importance of packaging and final production stages, in future studies it would be valuable to see these included for comparison with the impact of earlier production stages. It would seem that packaging and possibly unused product disposal may form a significant proportion of the lifecycle impact.

Packaging design and final production stages are designed particularly to support distribution and use. With future studies with other products, it would also be interesting to see the relative impacts allocated to distribution, storage, use and disposal, where packaging and final production stages may have an even more pronounced downstream impact, such as temperature sensitive products or products whose chosen delivery mechanisms result in fugitive GHG emissions in use and disposal.

Once again, we concur with Reviewer #2 and we have included a truncated version of their suggestion in the manuscript.
Page , paragraph . “The environmental effects of drug distribution, storage, use by clinicians (including syringes etc.) and hospital waste disposal, also require exploration.

Reviewer: 3
Reviewer Name Jodi Sherman

Institution and Country: Yale University, School of Medicine, Department of Anesthesiology

Please state any competing interests or state ‘None declared’:
None declared

Please leave your comments for the authors below
McGain Morphine LCA comments

General Comments:
- The article addresses an important and novel topic to health care and global health, the climate emissions that stem from pharmaceutical drugs using morphine as a key example. The authors do a reasonable job of making this case, though need to improve upon their justification/methods for their focus on Australia.

We thank Dr. Sherman for her thoughtful queries. We are actually quite content that our source data are robust as SunPharma (and formerly GSK) produces more than 25% of the world’s licit morphine.

Consider if a life cycle was performed of 30% of the world's propofol supplies, or a similar amount of the world's steel supply. One would be content that this represented a considerable portion of the total.

Page 5, paragraph 3, Introduction.
"We undertook a 'cradle-to-gate' LCA of morphine with GSK (Glaxo Smith Kline) and Baxter, both large, international pharmaceutical companies. Three companies in Australia produced 37% of the world's licit morphine, the majority of which (>25%) was produced by GSK.28 Baxter was the only Australian manufacturer of the 100mg morphine in 100mL bags. A cradle-to-gate LCA examines a product's life cycle from beginnings to exit from the 'factory gate', and does not include the syringes, intravenous fluid giving sets etc. used by a clinician when administering the intravenous morphine to the patient."

Are there only two manufacturers in Australia that supply 50% of the global licit supply? Are they the only suppliers for Australia?
There are in fact three manufacturers of opiates in Australia; GSK, Tasmanian Alkaloids and TPI Enterprises. SunPharma purchased their opiate processing facilities from GSK (Glaxo Smith Kline) in September 2015. TPI Enterprises is relatively small, producing less than 2% of the world's licit morphine.

Australia provides 50% of the world's bulk licit opiates and 37% of the world's licit morphine (Ref. 23, United Nations International Narcotics Control Board 2014. Narcotic Drugs. Estimated World Requirements for 2015, Statistics for 2013 [Available from: http://www.incb.org/documents/Narcotic-Drugs/Technical-Publications/2014/Narcotic_Drugs_Report_2014.pdf.).
There are a number of suppliers of morphine in Australia (e.g. Baxter Australia, DBL (Hameln).

Where are the other suppliers?
There are other companies in multiple countries (USA, Europe, etc.) that then package the bulk morphine from Australia and elsewhere into an oral or intravenous preparation (in a manner similar to what Baxter Australia does with the bulk morphine).

On page 5, paragraph 3 we make note of GSK's morphine production
"Three companies in Australia produced 37% of the world's licit morphine, the majority of which (>25%) was produced by GSK.28"

- The single greatest obstacle to understanding the environmental emissions of pharmaceuticals (and also devices) is the proprietary nature of synthesis. Standard portions of the manufacturing process, namely the active pharmaceutical ingredient, have been published. However, how ingredients are put together is confidential. Industry publications of their LCAs therefore cannot be verified, which is a weakness and primary justification for the study. The authors need to do a better job of spelling this out clearly for the readers. In fact, this should be the entire frame of their paper.

We agree have improved the justification for our study as suggested by Reviewer #3.
Page 4, paragraph 2, Introduction.
"…How ingredients are put together, however, is less clear and industry LCA publications cannot be verified. A large majority of a drug's environmental effects are due to the manufacture of the actual drug that doctors' prescribe, compared with producing the precursor ingredients.20 The primary aim of this study was to know further about the entire environmental effects of a drug as used by clinicians."

- The paper would be more readable if methods and results were broken down by subheadings for the respective stages: farming, extraction, preparation.

Pages 9-13 of the Methods and Results sections have subheadings as follows to improve readability:
“Farming, pelletising and transport
Bulk morphine manufacture
Mixing, filling, sterilisation and packaging”.

- There is virtually no discussion of non-CO2 emissions, and the paper would be much clearer if it stayed focused on just the CO2 emissions and the remaining emissions are moved to a supplemental section.

We found that the non-CO2 emissions stemming from the production of 100mg of morphine were minor, thus we did not devote much of the Discussion to non-CO2 emissions.
Page 11, paragraph 4, Results. “We have focused upon CO2 emissions, and provide further information regarding other environmental impacts in Supplemental Table 1 with associated documentation.”

- The authors struggle to contextualize their findings. While there is good national data on licit opioid requirements, the proportional breakdown of the types of formulations is never made clear. They rightfully try to compare their findings to the UK, but do so in a convoluted way with only a modest caution. They look at expenditures from the UK SDU on morphine to come up with a percentage of daily UK citizen CO2 contribution, and compare to their process results and findings of daily Australian citizen CO2 contribution, to say they are similar and therefore their results are a little verified. This metric makes no sense. Instead they ought to derive the weight-based emissions from the UK SDU economic method and compare that to their findings.

Providing detailed data about drug manufacture has rarely been published in the medical literature thus we have found it somewhat challenging to contextualize our results with other drugs and with the carbon footprint of an entire nation’s drug use.

We agree with Reviewer #3 that it would be best to delete…” The estimated yearly CO2 emissions in 2015 for all NHS pharmaceutical use in England was approximately 3,500,000 tonnes.5 The CO2 emissions arising from UK morphine use would thus be 1/265th of the total drug CO2 emissions for England as this is confusing input-output LCA data with our process based data.”

Page 14, paragraph 2, Discussion.
“We deliberated what the wider environmental ‘carbon impact’ of a nation’s morphine production would be, but caution that such considerations would likely be inaccurate due to the lack of robust data. The total UK requirements for morphine in 2015 were estimated to be 6,498 kg,23 which (if entirely intravenous) would lead to 13,250 tonnes of CO2 emissions. Whilst this is an over-estimation (i.e. less CO2 produced from oral morphine), the CO2 emissions of i.v. morphine would be equivalent to an annual usage of 4,400 average Australian cars.35”

We have deleted all reference to input-output LCA analysis as we agree with Reviewer #3 that this is confusing and may not make sense.
Page 14, paragraph 3, Discussion, (DELETED).
“The UK’s Sustainable Development Unit found that approximately 20% of the entire carbon footprint of England’s National Health Service was due to drug production and use.4 There are differences in the methods of input-output LCAs7 compared with our process based LCA. Essentially an input-output LCA is based upon the financial transactions between sectors in the economy, calculating carbon and other environmental impacts for each sector, and associating this with their final financial value (e.g. kgCO2/£). The UK England purchase costs for morphine as a proportion of the total pharmaceutical purchases for England in 2014 were £44 million of £8.9 billion37 (i.e. 1/250th or 0.4%).”

• The final life stage of the 100mg/100ml morphine manufacturing--preparation and packaging--is significant, so it shouldn't be left out. They do some hand waving about how other preparations are likely comparable, and multiply by Australian national Yet they only have data from one type of formulation 100mg MSO4/100ml NS. They mix multiple methods to justify the reasonableness of their extrapolation. The method here is convoluted. Maybe, if they could clarify this more it might fly.
We have simplified our manuscript and removed some of the discussion as suggested by Reviewer #3. We agree that we have data for only one type of form of morphine. Nevertheless, we think it is important that we compare our study and the 'packaging study' by Belboom: the message here is as the packaging in both studies forms a very important source of CO2 emissions.
Page 15, paragraph 2 (DELETED). "This approximation gives morphine's CO2 emissions as a proportion of total pharmaceutical CO2 emissions as similar to that which we estimated (1/265th), although we caution any further comparisons due to contrasting approaches to life cycle methods and differences between oral and intravenous morphine."

• This is not a pure process LCA, e.g., the authors use economic input-output for part of their analysis of GSK processes in order to attribute emissions between poppy extracted pellets and seeds.
The life cycle assessment is solely process based, with no economic input/output data, thus this is not a hybrid LCA. We give further clarification of the process of allocation as defined in the International Organization for Standardization.

Page 7, paragraphs 4 and 5, and page 8, paragraph 1, Methods.
"In process based LCA 'allocation' is required when a single process produces multiple outputs so that environmental effects can be allocated to each output. ISO 14044 (4.3.4.2 Allocation procedure)29 gives a stepwise process in dealing with multi-output processes, (1) avoid allocation through dividing processes, (2) allocate based on physical relationships such as mass, or (3) allocate by other relationships such as financial value.

There are two multi-output processes in morphine's manufacture by GSK: pelletising, which produces poppy straw pellets (for opiates) and poppy seeds (for food); and the concentrated poppy straw process that produces morphine, codeine, oripavine and thebaine. We were unable to avoid allocation by dividing the processes (a single process provides poppy straw and seeds). Further, a physical relationship (mass) did not capture the economic reality of why poppies were grown. Farmers grew poppies for the opioid content, not the poppy seeds - pharmaceutical companies were not about to grow opium poppies so they could supply the food market. Therefore we followed step three of ISO 14044 and allocated based on financial value.29 The environmental effects were allocated based upon the market value price (i.e. price/kg multiplied by kg mass) for each output. For each process we calculated a weighted average based on annual production data from 2012 and 2013, and this was modelled in SimaPro.

Later on, (in the discussion where it's location is suspect) they include results on analysis of glass ampoule packaging. They bring in a bit of their own process study of the glass ampoule packaging in the discussion section (?!) when they could just use it in the body of their paper and call this a hybrid LCA (which it already is.)
We have moved our minor work measuring the packaging associated with a 10mg glass ampoule of morphine to the Methods and Results as suggested. We note similarly to our responses to prior questions that these data does not make our process based LCA a hybrid LCA.
Page 11, paragraph 3, Methods.
"Packaging associated with a 10mg morphine glass ampoule
We did not find a manufacturer willing to provide information regarding the manufacture of 10mg morphine glass ampoules. Nevertheless, we did weigh the packaging associated with such 10mg

morphine ampoules at the hospital. We also obtained annual hospital morphine usage data."

Page 14, paragraph 4, Results.
"Packaging associated with a 10mg morphine glass ampoule
We estimated that the packaging masses associated with 10mg morphine ampoules were; one glass ampoule (1.9g), one plastic polypropylene tray (0.6g), and cardboard and paper (1.8g). In looking at the environmental effects of the packaging only this contributed 6.9g CO2, i.e. more than twice the CO2 emissions compared with the 10mg bulk morphine (2.4g CO2 or 1/10th of 24g CO2 from 100mg bulk morphine) itself. The total amount of intravenous morphine used for the financial year ending the 30/6/2015 at the 300-bed Footscray hospital was 430g."

Page 15, paragraph 1, Discussion.
"Using Belboom's study30 as a proxy for final formulation, if 10mg of our bulk morphine (1/10th of 24g CO2 = 2.4g CO2) was filled in a glass vial the related CO2 emissions would be 65g + 2.4g= 67.4 g CO2, with the vial and final formulation contributing 96%, and the bulk morphine sulphate 4%. Such results are in the same order of magnitude to our findings, but we caution close interpretation."

Comments by Section:
Strengths/weaknesses

- Remove statements in Strengths (and also Conclusion section) "… one of the very few….", or "….the only…", or similar type statements.

We have removed such statements.

- The methods for extrapolation to Australian national estimation are problematic, and may need to be removed if they can't be fixed

It is unclear to the authors why extrapolation to the Australian national CO2 emission estimates are problematic and need to be fixed. Australia is a signatory to the Kyoto protocol and provides robust national CO2 emissions. We have used reputable references for average Australian CO2 emissions (agreed by Reviewer #1 to be quite high, but correct and similar average American citizen's CO2 emissions). EcoInvent and GABI (LCA software and inventories) rely upon such national data when calculations of Australian CO2 emissions are performed.

- The very last point reads in a very confusing manner. In fact, that the authors worked with industry could be turned into a paper strength.

We have indicated that our study's strength stems from industry collaboration.
Page 16, paragraph 2, Discussion.
"We have shown from our study of 100mg morphine in plastic bags that 'commercial in confidence' concerns by pharmaceutical companies to LCA can be solved through collaboration leading to robust, publicly available data."

Nevertheless, we remain concerned that there is such little research in this field due particularly to industry intransigence.
Remainder of the same paragraph on page 16…
"Nonetheless, we were unable to obtain data regarding 10mg sterile morphine ampoules. As clinical end users of pharmaceuticals it is incongruous that we are unable to obtain information regarding the environmental effects of drugs we are administering to patients, and concerted advocacy efforts by medical colleges and associations to ask for such information from pharmaceutical companies could assist further research."

Abstract

- This is not ‘cradle-to-grave’ in that it is limited to manufacturing, even if authors were to call it such within the systems boundary of manufacturing. There appears to be no overt accounting of use/reuse (e.g. solvents) or waste management, and so it’s hard to even call it ‘cradle-to-gate’. Authors need to be more clear on use/reuse and waste phases to call it the latter.

We thank Reviewer #3 for our oversight as this study is indeed “cradle-to-gate”.
Waste management is included within ‘Energy, waste and transport’ in the System Boundary (Figure 1). We make further note of waste management in the Methods.
Page 10, paragraph 1.
“Details of use/re-use of chemicals (including solvents) and water were obtained, including waste and sewage data.”

- This is not entirely process based, e.g. the authors use economic surrogate data for GSK pelletizing and poppy seed extraction. It is therefore appropriate to call this a hybrid LCA.

Our study is purely a process based LCA (see answer several questions previously). We have used factory economic data allocation for a process based LCA, not national economic sector data for an input-output LCA.

- The vast majority of the paper focuses on CO2e, and thus this ought to be named the primary outcome measure. All others are secondary, and indeed only given cursory space. The authors should strongly consider leaving out the secondary measures completely, or relegating them to the supplemental material as they do not appear to add anything to the paper and distract from the topic at hand.

We have addressed this concern previously. Our manuscript is focused upon CO2eq and we have relegated other information to Supplementary Table 1 with associated explanations.
The primary outcome measure was not purely aimed at discovering CO2eqs as: (1) this was not solely what we set out to do, and (2) researchers perusing PubMed or other search engines would not locate the other environmental effects of morphine production of our study if the heading/abstract had ‘carbon’ in lieu of ‘environmental’.

- It is unclear that the author’s achieved sufficient rigor to characterize their results in terms of an Australian’s daily CO2 emissions. While important to contextualize, this stretch may not be possible.

This query is similar to the previous: “The methods for extrapolation to Australian national estimation are problematic, and may need to be removed if they can’t be fixed.”
We have Australia’s officially reported per annum CO2 emissions and Australia’s officially reported population. We are unsure how we can achieve greater rigor in our normalisation number.

Introduction

- There is a more recent reference of the US healthcare footprint you should use, Eckelman in PONE.

We have replaced Chung and Meltzer’s article with the more recent reference by Eckelman and Sherman.

- It is incorrect to state that the UK SDU has developed a protocol to perform pharmaceutical LCAs. (IF they have, then what is it?) IT is correct to say that they have called for it.

Page 4, paragraph 1. We agree that this is not a protocol as such, but rather has been labelled as a guideline by the UK Sustainable Development Unit and have altered the wording as required.
Reviewer #2 (Jerome Baddley) may wish to clarify this further as he works for the UK SDU.
Reference 6 in the (original) manuscript was (and remains):
The Sustainable Development Unit UK. Greenhouse Gas Accounting Sector Guidance for Pharmaceutical Products and Medical Devices 2012 Nov. [Available from: http://www.sduhealth.org.uk/areas-of-focus/carbon-hotspots/pharmaceuticals.aspx.

• IF you are going to focus attention to Australian formularies, then you need to say something about the size of the Australian health sector. IF the carbon footprint is unknown, say so. At the very least you can describe the size in terms of national health care costs and percent of GDP, so we can begin to understand some comparatives between the US and the UK.
We have addressed the relative size of the Australian healthcare sector as suggested by Reviewer #3.
Page 4, paragraph1, Introduction.
"LCA has been used to estimate healthcare's entire 'carbon footprint', and has been found respectively to be responsible for 3% of England's,4 and 9.8% of the 2013 United States' CO2 emissions.5 The USA spends almost twice as much on healthcare (17.1%) as a proportion of Gross Domestic Product (GDP) as the United Kingdom (UK) (9.1%).6 Australian healthcare CO2 emissions are unknown, although healthcare costs are similar to the UK (9.4%of GDP).6"

• Please explain what an alkaloid is. How is this different from raw extracts?
Page 5, paragraph 1, Introduction.
"Australia produces approximately 50% of the global supply of licit opium poppy alkaloids (plant based nitrogen-containing organic compounds such as morphine)."

Raw material is now defined.
Page 7, paragraph 2, Methods.
"(i) raw material (plant based products, e.g. cellulose) extraction,…"

• Why are you aiming to quantify morphine's environmental effects? It is left un/understated why you are interested in CO2, water use, aquatic and terrestrial pollution.
We agree that we have understated why we are trying to quantify morphine's environmental effects and have elaborated upon why we undertook our study in the Introduction.
Page 4, paragraph 2, Introduction.
"How drug ingredients are put together, however, is less clear and industry LCA publications cannot be verified. A large majority of a drug's environmental effects are due to the manufacture of the actual drug that doctors' prescribe, compared with producing the precursor ingredients.21 It appears that the manufacture of all drug's collectively has a very large carbon footprint,4 although individual drug information is lacking.The primary aim of this study was to know further about the entire environmental effects of a drug as used by clinicians.We chose to study morphine as it was a commonly used drug, known worldwide, that Australia produced in considerable quantities, and that could be studied with the collaboration of supportive pharmaceutical companies."

• You move from Australia production of 50% of global alkaloids exported, to looking at Australian common preparations (ampoule and bag). You need to transition to/say more about the Australian health market if you want to focus on Australian preparations.
Thank you for highlighting this potential issue. The Australian health market is similar to that in the UK and countries with similar economic standing. It is correct though that the US healthcare system is an outlier in terms of cost as a % of GDP and we have noted this.
Page 4, paragraph 1, Introduction.
"The USA spends almost twice as much on healthcare (17.1%) as a proportion of Gross Domestic Product (GDP) as the United Kingdom (UK) (9.1%).6 Australian healthcare CO2 emissions are unknown, although healthcare costs are similar to the UK (9.4%of GDP).6 Further, Australian clinical practice broadly reflects that in the UK, Europe, and Canada, though it is less financially costly than healthcare in the USA."

Pharmaceutical preparations in Australia and the UK for example are similar (if not identical) to that

used in the UK (from Reference 40 in the manuscript- Medicines and Healthcare Products Regulatory Agency. British Pharmacopoeia. Appendix XVI D. Microbiological Quality of Non-sterile Pharmaceutical Preparations and Substances for Pharmaceutical Use. 2016 [Available from: https://www.pharmacopoeia.com/reference-standards).

- What is GSK and why did you enter in a study with them and Baxter?

Page 5, paragraph 3. "We undertook a 'cradle-to-gate' LCA of morphine with GSK (Glaxo Smith Kline) and Baxter, both large, international pharmaceutical companies. GSK produced 25% of the world's licit morphine.27 Baxter was the only Australian manufacturer of the 100mg morphine in 100mL bags."

Methods/Results: See general comments above

Discussion

- You introduce new methods and results here, namely the breakdown of the glass ampoule. Unless this is published, then it belongs either in the methods section or ought to be left out (see general comments above.)

We have addressed this concern previously and have moved such information to the Methods and Results as suggested.

VERSION 2 – REVIEW

REVIEWER	Hugh Montgomery United Kingdom I sit on the UK Climate and Health Council, and co-chaored the recent (and ongoing) Lancet commission on Climate and Health, but do not view such activity as 'competing'.
REVIEW RETURNED	01-Sep-2016

GENERAL COMMENTS	I think that this paper reads very well, and is acceptable for publication.

REVIEWER	Jodi Sherman Yale University, School of Medicine USA
REVIEW RETURNED	13-Sep-2016

GENERAL COMMENTS	Thanks again to the authors for tackling such an important topic as the environmental impact of pharmaceuticals, morphine as an example. This version is greatly improved upon. I still have a number of comments, that if addressed would strengthen the manuscript. Abstract: • Pg 2 line 34-35: clarify CO2 as CO2 equivalents for novice readers, also in results section. • 0.4% of an Australian's daily CO2 emissions seems VERY high. Please recheck your calculations, and/or consider leaving this out. Strengthes/limitations: • When you state that "total environmental effects…were small…," relative to what? Caution must be taken so that the authors don't diminish the importance of their work. This gives the impression that

	small pollution doesn't matter. In fact, there is a cumulative effect that is concerning. • Ought to be complemented with Australia's annual morphine usage—not just UK's. • That you did not look at other preparations is the major weakness, and warrants it's own bullet Introduction: • Pg 4, line 45, "…carbon footprint," you use reference 4. Would also recommend reference 5. It also true that the footprint for drugs is very large in the US. • "3 companies" is confusing, since all data from just 2. May simply call it 2 companies, and keep sentence on Sun pharmaceuticals, to make it less confusing. • Australia produce 37% of morphine supply to Europe, UK and elsewhere. Can you say what this absolute quantity this is since you have access to the company data? • Since Baxter is the only one to produce 100ml bags in Australia, and since that packaging is so substantial, could you say how much they produce annually since you have access to company data? • If the manufacturer sterilizes saline, whether or not drug is added, you may be able to potentially extrapolate to bags prepared outside of Baxter in your discussion section. Methods: • Pg 9, lines 51-58: This is confusing. Can you speak plainly to the % obtained outside of GSK, and simplify the paragraph? • Pg 10 line 35-36. It's great you weighed the materials directly. State which hospital for clarification. As to annual hospital usage data, this is irrelevant to your study so remove that line. Results: • Pg 11, Line 15: While I understand the calculation, 0.4% seems VERY large, and is very difficult to believe. You may have a propagation error, please double check your calculations. Consider leaving this out. • Your results on glass packaging are interesting. However, total amount of IV morphine used for Footscray is irrelevant to this study, please remove. Discussion: • Pg 13 line 10, remove the descriptives "small" and "very small" as this diminishes the importance of your work. You can say other impacts covered in the supplemental section and leave it at that. • I do not see Belboom's study in the references (listed as number 30). Please fix. • Pg 40, line 16-18, The Sherman study is cradle-to-grave, not a cradle-to-gate. Further, propofol is reported in units of time. Thus the authors can not extract a meaningful number that aids their readers here. The paragraph contributes to the discussion from a methodologic perspective and so I suggest contracting the sentence to read "…et al, examined drugs using SciFinder…." • Pg 40, line 25: It is not possible to compare a cradle-to-grave study results for an hour's worth of propofol, to an estimated case requirement for morphine multiplied by results from your cradle-to-gate study to try to demonstrate they are in the same order of magnitude. Really, what the authors need for their comparison is the LCI of propofol but this is not reported in their paper. If the authors were to communicate directly with Sherman, et al., they would learn that the LCI is estimated at 5kg CO2/kg propofol. However, this has not been published as such. • The comparison to Wernet, this is very helpful. It is confusing to read, however. Please simplify by using consistent units only, i.e. 240 g CO2/g of bulk morphine alone for the comparison. As the

	authors point out, this is an order of magnitude higher than Wernet's generic example (and also off by 2 orders of magnitude to Sherman's LCI results, not published.) The authors are strongly urged to review their original calculations for a potential propagated error. • Pg 41, line 8. Probably an overstatement to say that GSK and Baxter act with "environmental awareness." The greatest motivation is more likely for "resource conservation."

VERSION 2 – AUTHOR RESPONSE

Reviewer: 1

Reviewer Name
Hugh Montgomery

Institution and Country
United Kingdom

Please state any competing interests or state 'None declared':
I sit on the UK Climate and Health Council, and co-chaired the recent (and ongoing) Lancet commission on Climate and Health, but do not view such activity as 'competing'.

Please leave your comments for the authors below
I think that this paper reads very well, and is acceptable for publication.

Thank you very much Prof. Montgomery.

Reviewer: 3

Reviewer Name
Jodi Sherman

Institution and Country
Yale University, School of Medicine
USA

Please state any competing interests or state 'None declared':
none

Please leave your comments for the authors below
Thanks again to the authors for tackling such an important topic as the environmental impact of pharmaceuticals, morphine as an example. This version is greatly improved upon.

Thank you very much Prof. Sherman.

I still have a number of comments, that if addressed would strengthen the manuscript.

Abstract:
- Pg 2 line 34-35: clarify CO2 as CO2 equivalents for novice readers, also in results section.

Page 2 and beyond- 'equivalents (e)' added.
This has been altered as suggested by Reviewer #3.

• 0.4% of an Australian's daily CO2 emissions seems VERY high. Please recheck your calculations, and/or consider leaving this out.
The 204g CO2 e emissions from 100mg morphine production is 0.4% of an Australian's daily CO2 e emissions. This would indicate that an average Australian emits approximately 0.2kg X 1,000/4 = 50 kg CO2 e emissions per day, or 18.3 tonnes of CO2 e emissions per annum which is approximately correct. Nevertheless, we feel that our statement could be replaced by comparing the CO2 emissions of morphine production to another common activity, such as driving a standard car-
Abstract, Results, Page 2.
"Morphine sulphate 100mg in 100mL had a climate change effect of 204g CO2 equivalents (95%CI: 189g to 280g CO2), approximating the CO2 e emissions of driving an average car 1km."

Strengthes/limitations:
• When you state that "total environmental effects…were small…," relative to what? Caution must be taken so that the authors don't diminish the importance of their work. This gives the impression that small pollution doesn't matter. In fact, there is a cumulative effect that is concerning.
Page 3, Strengths/Limitations.
We have altered the manuscript to indicate the cumulative effect of worldwide morphine production.
"We completed a life cycle assessment of an identified drug that has worldwide use. The total environmental effects of 100mg of packaged morphine were similar to or less than travelling 1km in a standard car in all of the domains examined including the carbon footprint, toxicity, and water use. Nevertheless, when considering worldwide morphine usage, the environmental effects become significant.

• Ought to be complemented with Australia's annual morphine usage—not just UK's.
We examined the environmental effects of morphine use for the UK since the BMJ Open is a UK based journal. It is arguably most useful to give a perspective with just one country rather than several such as Australia and the UK, or even including the USA for example. We would be happy to include several countries, but a single national comparison was thought most pragmatic.

• That you did not look at other preparations is the major weakness, and warrants it's own bullet
Page 3, Strengths and Weaknesses. The following weakness has been added as suggested
• "We were unable to obtain data regarding the environmental effects of another common preparation of morphine- i.e. a 10mg morphine ampoule, also for intravenous usage."

Introduction:
• Pg 4, line 45, "…carbon footprint," you use reference 4. Would also recommend reference 5. It also true that the footprint for drugs is very large in the US.
Page 4, second paragraph. Altered as suggested by Reviewer #3.
"It appears that the production of all drugs collectively has a very large carbon footprint,4 5…"

• "3 companies" is confusing, since all data from just 2. May simply call it 2 companies, and keep sentence on Sun pharmaceuticals, to make it less confusing.
Page 5, paragraph 3.
We hope that the following sentence clarifies any misunderstandings,
"Three companies in Australia produced 37% of the world's licit morphine, the majority of which (>25%) was produced by GSK.28 Baxter did not manufacture morphine, but was the only company that packaged and sterilised the 100mg morphine into 100mL bags in Australia."
It would be incorrect to state that only two companies in Australia produced 37% of the world's licit

morphine, but mentioning the other two manufacturers of bulk morphine is not required.

- Australia produce 37% of morphine supply to Europe, UK and elsewhere. Can you say what this absolute quantity this is since you have access to the company data?

We are unable to give the absolute quantity as SunPharma is unable to disclose such confidential information. Note however, that we did write that the global legal production of morphine in 2013 was 523 tonnes in the Background which will give a reasonable approximation.

- Since Baxter is the only one to produce 100ml bags in Australia, and since that packaging is so substantial, could you say how much they produce annually since you have access to company data?

Page 9, paragraph 5. Methods. We have included information about the number of bags sterilised by Baxter in Australia per annum.

"In 2015, Baxter Australia sterilised approximately 32,000 bags of morphine for intravenous use."

- If the manufacturer sterilizes saline, whether or not drug is added, you may be able to potentially extrapolate to bags prepared outside of Baxter in your discussion section.

Baxter Australia sterilises approximately 150,000 intravenous fluid bags per day. SunPharma does not sterilise saline. We are unable to make an educated extrapolation to the number of morphine bags prepared beyond Baxter.

Methods:

- Pg 9, lines 51-58: This is confusing. Can you speak plainly to the % obtained outside of GSK, and simplify the paragraph?

Page 9, final paragraph. As suggested by Reviewer #3 we have simplified the paragraph in question as it is relatively peripheral to the main purpose of the manuscript. Since we do not know the proportion of GSK's/SunPharma's morphine that ends up being indirectly purchased by Baxter it is better to remove any discourse on the topic.

"Baxter Australia purchased bulk morphine which didn't require further chemical modification. Due to contractual arrangements the morphine received by Baxter Australia was not directly sourced from GSK. (GSK did supply Baxter with bulk morphine previously)."

- Pg 10 line 35-36. It's great you weighed the materials directly. State which hospital for clarification. As to annual hospital usage data, this is irrelevant to your study so remove that line.

Page 10, paragraph 3, Methods. We have edited the manuscript as suggested by Reviewer #3.

"…Nevertheless we did weigh the packaging associated with such 10mg morphine ampoules at Footscray hospital."

We have removed the line "We also obtained annual hospital morphine usage data."

Results:

- Pg 11, Line 15: While I understand the calculation, 0.4% seems VERY large, and is very difficult to believe. You may have a propagation error, please double check your calculations. Consider leaving this out.

Page 11, paragraph 2, Results.

(The same concern as per the Abstract, Results, Page 2).

'The average Australian is responsible for 18.3 tonnes of CO_2 per annum,34 indicating that this 100mg of morphine producing 204 g CO_2 is approximately 0.4% of daily per capita Australian CO_2 e emissions, and equivalent to the CO_2 e emissions of driving an average car approximately 1km.35"

The 204g CO_2 e emissions from 100mg morphine production is 0.4% of an Australian's daily CO_2 e emissions. This would indicate that an average Australian emits approximately 0.2kg X 1,000/4 = 50

kg CO2 e emissions per day, or 50 kg X 365 =18.3 tonnes of CO2 e emissions per annum which is approximately correct. Nevertheless, we feel that our statement could be replaced by comparing the CO2 emissions of morphine production to another common activity, such as driving a standard car. We have rechecked our calculations and cannot see any errors.

- Your results on glass packaging are interesting. However, total amount of IV morphine used for Footscray is irrelevant to this study, please remove.

Page 12, final paragraph, Results. We have removed the data about the total amount of morphine used for Footscray hospital.
"The total amount of intravenous morphine used for the financial year ending the 30/6/2015 at the 300-bed Footscray hospital was 430g."

Discussion:

- Pg 13 line 10, remove the descriptives "small" and "very small" as this diminishes the importance of your work. You can say other impacts covered in the supplemental section and leave it at that.

Page 13, paragraph 1, Discussion.
We have removed the absolute descriptive small. We have added the comparator noted in Supplemental Table 1 (burning one litre of petrol) to give the reader some perspective as to the environmental effects of producing 100mg of morphine.

"The environmental effect of producing 100mg morphine was 204g CO2 e for climate change. Other environmental effects examined were considerably smaller than burning one litre of petrol for car transport, except for ozone depletion, though even this was but 0.04% of the ozone depleting effects arising from an average Australian's daily activity (Supplemental Table 1)."

- I do not see Belboom's study in the references (listed as number 30). Please fix.

Page 14, paragraph 1, Discussion.
Thank you. This error has been corrected and Belboom's study is now Reference #38.

- Pg 40, line 16-18, The Sherman study is cradle-to-grave, not a cradle-to-gate. Further, propofol is reported in units of time. Thus the authors can not extract a meaningful number that aids their readers here. The paragraph contributes to the discussion from a methodologic perspective and so I suggest contracting the sentence to read "…et al, examined drugs using SciFinder…."

Page 14, paragraph 2, Discussion. We have contracted the sentence and amended the manuscript as suggested
"A recent cradle-to-grave LCA of anaesthetic gases by Sherman et al examined drugs using SciFinder®39 (CAS web-based chemistry database, American Chemical Society, USA) as direct data were unavailable from the manufacturers."

- Pg 40, line 25: It is not possible to compare a cradle-to-grave study results for an hour's worth of propofol, to an estimated case requirement for morphine multiplied by results from your cradle-to-gate study to try to demonstrate they are in the same order of magnitude. Really, what the authors need for their comparison is the LCI of propofol but this is not reported in their paper. If the authors were to communicate directly with Sherman, et al., they would learn that the LCI is estimated at 5kg CO2/kg propofol. However, this has not been published as such.

Page 14, paragraph 3, Discussion.
We have deleted the following sentence as we agree with Prof. Sherman that it is impossible for us to make comparisons with the study by Sherman et al.
"Despite a direct comparison being difficult, propofol's CO2 e emissions22 were in the same order of magnitude as our findings for 100mg morphine, given that most surgical operations require in the order of 10mg morphine (1/10th of 204g CO2)."

- The comparison to Wernet, this is very helpful. It is confusing to read, however. Please simplify by using consistent units only, i.e. 240 g CO2/g of bulk morphine alone for the comparison. As the authors point out, this is an order of magnitude higher than Wernet's generic example (and also off by 2 orders of magnitude to Sherman's LCI results, not published.) The authors are strongly urged to review their original calculations for a potential propagated error.

We have reviewed our calculations and cannot find any errors. This study has in particular, involved chemists, chemical engineers and a life cycle assessor who have access to actual data about morphine manufacture from two pharmaceutical companies. Wernet also had access to pharmaceutical company information. Our findings are in the same order of magnitude as Wernet et al, though we do caution differences between drug production which may lead to considerably different environmental footprints.

Page 14, paragraph 3, Discussion. The manuscript has been altered as suggested by Reviewer #3.
"Wernet et al studied the entire synthesis of a de-identified active pharmaceutical ingredient and found its life cycle produced 68g CO2/g drug.21 Wernet's study did not include the final sterilisation processes nor packaging. Our study found that bulk morphine (i.e. not including sterilisation and packaging) produced 240g CO2/g morphine, considerably more than Wernet's unidentified drug. We caution though that there may be considerable variation in processing between different drugs."

- Pg 41, line 8. Probably an overstatement to say that GSK and Baxter act with "environmental awareness." The greatest motivation is more likely for "resource conservation."

Page 15, paragraph 1, Discussion.
The manuscript has been edited as suggested by Reviewer #3.
"Perhaps we have underestimated the environmental effects of drug production since GSK and Baxter act with resource conservation in mind."