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**From:** Sturgess Nick GBAP  
**Sent:** Friday, August 12, 2005 1:14 PM  
**To:** Elliott Barry GBAP  
**Subject:** RE: Olfactory transport to the brain

Barry,

I've not had much of a response from Paul or Matt except the list of references that Paul forwarded. The following are therefore some of my thoughts on this issue, and as such, I've not managed to formulate a definitive position since I think more input from others more knowledgeable than myself may be required.

Having read through some of the information provided by Paul, my opinion is that there certainly is a potential for PQ to be transported to the olfactory bulb if the nasal mucosal epithelium comes into contact with PQ. This view is based upon experimental data obtained following nasal exposure to some metals and compounds such as dopamine and morphine. The mechanism involved seems to be transfer along the olfactory nerve pathway, via some form of axonal transport, directly to the olfactory bulb into the brain, thereby circumventing the BBB. Effectively it would seem that there is a transport pathway from the nasal cavity to the olfactory bulb part of the brain. Interestingly, it would appear that metals or compounds don't readily pass to adjacent brain areas once they have reached the olfactory bulb - for example, in studies with Mn, the metal was detected in the olfactory bulb but not the striatum. Whether the same would happen with PQ is open to debate.

The kinetics of this transport process seem quite rapid, since studies with morphine reveal the presence of compound in the olfactory bulb within minutes (15-60 min) following introduction into the nasal cavity. In studies where the % of the total exposure dose in the olfactory bulb has been determined, it is <10% (and in some cases <1%) of the total dose. It should be possible to estimate what volume of PQ spray (based upon droplet size) that would need to be inhaled into the nasal cavity to give a particular brain exposure (say 1 mg/kg) which is the ip LOEL for neuronal cell loss in the mouse. Perhaps this calculation should be done based upon a conservative estimate of 10% of the total dose gaining access to the brain. Hopefully the number will demonstrate that the nasal cavity would need to be exposed to a massive volume of PQ spray (which would be unlikely to ever occur in reality), to give a brain exposure equivalent to the ip LOEL and this will give us some comfort.

In the light of all this, it is difficult to develop a more definitive defensive position for PQ owing to the lack of definitive quantitative experimental data measuring olfactory bulb concentrations of PQ following nasal exposure. If the request for DEFRA proposals are taken up by a research group, then this is one area where some data will almost certainly be generated.

Perhaps Martin Wilks / Clive Campbell should also be consulted for their views on this, since I find it hard to believe this issue has not been considered before. I suspect the droplet size issue and volume of spray required to be inhaled will be our best defence.

Nick.

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**From:** Elliott Barry GBAP  
**Sent:** 05 August 2005 16:26  
**To:** Sturgess Nick GBAP  
**Cc:** Hext Paul GBAP; Jacobsen Matthew GBAP  
**Subject:** Olfactory transport to the brain

<< File: Project specification\_re-tender\_parkinsons\_mechanistic\_.doc >>  
Nick,

The DEFRA proposed mechanistic work (enclosed) has a part (highlighted in the document) on possible entry into the brain via the olfactory bulb (abstracted below).

.....Chemicals could also enter the brain without having to cross the blood brain barrier. Olfactory neurones are in contact with the environment via the olfactory epithelium. Certain chemicals have been shown to be transported along olfactory neurones to the olfactory bulb and then to other areas of the brain. Work with manganese (reviewed at <http://www.le.ac.uk/ieh/pdf/W17.pdf> ) has shown transport to the olfactory bulb to be dependent on particle size and solubility. The potential for olfactory transport of pesticides does not appear to have been investigated specifically.....

Could you consider the possible relevance of this sufficient for us to have a position on applicability to PQ. **Paul and Matt**, please let Nick have comments from your perspectives (inhalation/anatomy). Relation of olfactory bulb and neurones to the blood brain barrier would be important.

[With PQ, two other elements may be, or could be considered to be, relevant in this context:

- We say that PQ spray generates large droplets, that are not respirable - and so may be trapped in the nose in reasonable amounts?
- We know that in some circumstance nosebleeds can occur with PQ application (albeit likely following introduction of fingers into the nose), and this may indicate abraded skin, with more rapid penetration of materials?]

I would not see this as a major review, but intended as one for internal positioning at this time.

With thanks,

Barry