Electronic Cigarettes and Airway Infections – Update

8. FEBRUARY 2015 BY BERND MAYER — 25 COMMENTS

Recently it has been reported that mice exposed to nicotine containing vapor of electronic cigarettes exhibited reduced immune defense to bacterial infection (Sussan et al., 2015). From the mouse data, the authors infer that consumption of electronic cigarettes may compromise the immune response of humans. This result attained considerable media coverage and is expected to be embraced by health authorities eagerly searching for detrimental effects of e-cigs to justify strict regulations and bans.

However, nobody would have cared about this result, and no journal would have accepted the paper if the authors had replaced "electronic cigarettes" in the title by "nicotine". It has been known for decades that nicotine has anti-inflammatory effects associated with mild immune suppression in mice and rats (e.g. Roszman et al., 1975, Petro et al., 1992, Geng et al., 1996, Kalra et al., 2000, Navarro et al., 2001, Matsunaga et al., 2001, Kalra et al., 2002, Kalra et al., 2004, Skok et al., 2005, Sadis et al., 2007, Fujii et al., 2008, Hirschburger et al., 2009, Tyagi et al., 2010, Wang et al., 2010, de Lucas-Cerillo et al., 2011, Kolgazi et al., 2013, Nemethova et al., 2013).

According to these and many more published papers, the anti-inflammatory effects of nicotine are mainly mediated by inhibition of release of pro-inflammatory cytokines, an effect typically associated with suppression of immune function. Based on these observations, drugs stimulating nicotinic receptors on non-neuronal, in particular immune cells were considered as being useful for the therapy of inflammatory and infectious diseases, such as rheumatoid arthritis, inflammatory bowel disease, inflammatory disorders of the brain, and sepsis as well as metabolic diseases and cancer immunotherapy (e.g. Supori, 2002, Wang et al.,2004, McGilligan et al., 2007, Shi et al., 2009, Green et al., 2010, Cui & Li, 2010, Gao et al., 2011, Somm, E., 2014).

These reports may look promising, but immune function of mice and rats translates poorly to the human condition, a well-known nuisance for experimental immunologists involved in drug development (see e.g Mestas & Hughes, 2004, Shai et al., 2013). So far, no nicotinic receptor agonist has made it to market, and there is not a trace of evidence that nicotine replacement therapy is associated with impaired immune function. Thus, there is no reason to worry that nicotine consumption, either by consumption of FDA-approved medicines or inhalation of nicotine containing vapor, might cause significant immune suppression.

In a previous blog article, I presented the results of a survey on the frequency of airway infections (common cold) among e-cig users who had not been smoking for at least two months. Meanwhile, the number of votes has more than doubled (from 307 to 657) – with no significant change in outcome:

total: n=657 (100 %), infections decreased: 441 (67.1 %), no change: 193 (29.4 %), infections increased: 23 (3.5 %)

These results may still be judged as anecdotes without scientific value. However, the data are surprisingly robust and unequivocally demonstrate the experienced benefit of switching from tobacco smoking to vaping, with almost 70 % of users reporting decreased incidence of airway infections and hardly any reports of worsening.
The improvement could be simply due to discontinuation of smoking but additional beneficial effects of inhaled propylene glycol are also conceivable. Regardless the underlying cause, the results obtained by Sussan et al. with nicotine-exposed mice are in sharp contrast to the highly positive experience of humans switching from smoking to vaping.

Filed Under: **Blog** Tagged With: **airway infection**, **electronic cigarettes**, **immune function**, **inflammation**, **nicotine**

About Bernd Mayer

Dedicated to science, critical thinking, and scientific education of young people. Fighting pseudoscience and all kind of esoteric junk.

Comments

Frank Baeyens says
8. February 2015 at 17:51

Excellent analysis! Bernd, maybe you might also include a comment on this related Feb 6th PlosOne paper http://journals.plos.org/plosone/article?id=10.1371/journal.pone.0116732 ?

Reply

Bernd Mayer says
8. February 2015 at 18:52

They are faster in publishing junk than I am able to read it. Intriguingly, the first paper is consistent with an anti-inflammatory effect, whereas the next one suggests increased inflammation. Average: no effect. 🙂
Unfortunately, they all consistently refrain from comparing ecig vavor with tobacco smoke. Without this comparison, it is not possible to judge the magnitude and thus relevance of the oberved effects.

Reply

Licensing of Fruit Flavors and Colored Devices

erick says
8. February 2015 at 18:28

Airway infections was also very low when I was smoking. So can't really say if you get it less. But the effect when you get it is much less. 36 year smoker and 1+ year vaper now.

Reply

Kate Ackerman says
8. February 2015 at 18:41

THANK YOU Dr Mayer! I really appreciate that you are standing up and pointing out that the emperor's new clothes (no matter how many of his advisors say he "looks great" is really buck naked. The deception attempts in scientific circles on ecigs are staggering. Who's bankrolling all this? Or is it just a trend? Or was it "take your toddlers to work week" in scientific circles, and "let them make their own scientific experiments".

Reply

Bernd Mayer says
8. February 2015 at 19:16

Scientists need publications to get tenure, grant money and reputation. At present junk papers appear to be acceptable for reviewers and journal editors as long as the results support the anti-ecig policy of WHO, FDA & Co.

Reply

Margaret Hermon says
8. February 2015 at 20:23

I know I'm just another anecdote but as an asthmatic and COPD (mild) patient the following may be of interest.
Prior to 2010 I had at least 2 – 3 infections per annum requiring antibiotics and steroid tablets and emergency admission for oxygen the last time – which was when I realised I had to try, yet again, to stop smoking. On Jan 28th 2010 I got my first e-cig and, primitive though it was, have never smoked since. Until April 2014 I had not one single infection. It may be coincidence but I had dropped my ratio of pg to vg from 70/30 to 50/50 and I picked up a bug! Still no asthma attack though; I have just had another bug that has been rife and got over it in two weeks and just one course of Amoxycillin 500 – others have reported 4 and 5 weeks and several courses of ABs. Needless to say I have now returned to 70/30%! My asthma medication is now a token 2 puffs of iprotropium at night as against 2 puffs 3 times a day pre 2010; no longer need salmeterol or ventolin, so I'm a healthy happy anecdote.

Reply

Inge says
8. February 2015 at 23:21

That's my story. I Vapeshake now for 7 years and also nomore prednison pills for the atshma

Reply

Inge says
8. February 2015 at 23:23

I mean offcourse i vape for 7 years and the story could be mine

Reply

Zac says
11. February 2015 at 15:32

I am an asthmatic as well and smoked for about 9 years. I was constantly battling respiratory infections and severe attacks. After switching to vapor, I've not had anything worse than a head cold. In fact, I got over a cold in 2 days that other people have been battling for a week or more.

Reply

Luc Dussart says
9. February 2015 at 0:52

Pr Molimard conducted a small survey in France. Here are the results (pls translate) :

"Concernant la fréquence et la durée des rhumes dont les vapoteurs ont souffert, en comparant les périodes avant et après qu'ils aient commencé à utiliser leur vaporisateur personnel, les résultats bruts sont en faveur mon hypothèse, basée sur l'action anti-bactérienne et antivirale du propylène-glycol, conjuguée avec celle de la chaleur, que détestent les virus.
"Il y a eu en moyenne seulement 1,28 rhumes contre 5,96 dans une même période avant début du vapotage. Ils ont duré en moyenne 4,24 contre 7,32 jours.
"Statistiquement, il y a moins d'une chance pour mille que ces différences puissent être le fait du seul hasard. "
http://www.unairneuf.org/2015/01/rhume-vapilo-molimard.html

If I understand him correctly, two factors are involved :
1°) Propylene glycol own properties against viruses and bacteria
2°) The PG is heated, and that should greatly contribute to the result.

Reply

Bernd Mayer says
9. February 2015 at 8:46

Thank you for the information. Unfortunately I am not particularly well in French. Would be interesting to see the data that led Dr. Molimard to his conclusions.

Reply

Luc Dussart says
9. February 2015 at 10:40

This is a small sample, sufficient to validate an hypothesis but not to conclude. I'll mail the data to you. Please take note also that Pr Molimard is a (retired and respected) medicine Professor, cf. his bio on Wikipedia : fr.wikipedia.org/wiki/Robert_Molimard

Reply

ezmoose says
9. February 2015 at 4:54

The flip side is that there have been few E Cigarette Adverse Events Reported to the FDA

"A surveillance system of adverse events has been developed by the FDA, which identifies safety concerns in relation to tobacco products. Since 2008, 47 adverse events were reported for ECs [Chen, 2013]. Eight of them were serious events such as hospitalizations for pneumonia, heart failure, seizures and hypotension and burns. A case of second-degree burns was caused by a battery explosion, which is generally a problem observed in lithium batteries and has occurred in other products (such as mobile phones). The author emphasized that the reported events were not necessarily associated with EC use but may have been related to pre-existing conditions or other causes. No condition was characteristically associated with EC use."

Safety evaluation and risk assessment of electronic cigarettes as tobacco cigarette substitutes: a systematic review
http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4110871/

The reports have been meager at best. I don't doubt that some may experience an allergic reaction to say Propylene Glycol; some people are allergic to milk. Or that a preexisting condition could be aggravated by the inhalation of vapor. However, many of the reports can be dismissed as weak associations.

"I was sitting next to a person who was puffing on an e cigarette for a few hours in a closed room and developed bad headache, inflamed sinuses and eye irritation. I left work sick and symptoms did not resolve for about 24 hours. The day after, my throat became sore and now I have cold like symptoms."

http://www.fda.gov/downloads/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/AbouttheCenterforTobaccoProducts/U

Translation: I don't like E-Cigarettes and I have a cold.

Reply

Frank Baeyens says
21. February 2015 at 1:37

Interesting comments....

http://www.plosone.org/annotation/listThread.action?root=85496

Of Mice and Men

Posted by amukhin on 19 Feb 2015 at 19:33 GMT

We read this article with great interest, as it addresses the important topic of developing a model for the evaluation of the safety of electronic cigarette (e-cig) use. The authors report that e-cig vapor at some level of exposure may not only cause lung inflammation but reduces anti-bacterial and anti-viral defenses.

One of the critical problems in the development of any animal model for human pharmacology and toxicology is determining the animal doses or the level of exposure that will adequately reflect human conditions. In the described model the authors used the level of e-cig vapor exposure in mice resulting in a blood cotinine level that matches the level observed in regular e-cig users. The use of such a level of exposure in the animal model would be valid only if the intensity of nicotine and cotinine metabolism in mice and in humans were comparable. In reality the metabolism of both compounds in mice is much faster than that in humans. For example the half-life value of nicotine in mice is about 8% of that in humans (9 min vs. 120 min) and the half-life value of cotinine in mice is only about 4% of that in humans, 0.6h vs. 16 h (Siu & Tyndale, 2006; Benowitz et al., 2009). Therefore the nicotine exposure of mice will be much higher than that in humans to produce the same level of blood cotinine.

Since the proposed model may be used in further studies and the results of the study could be interpreted by people who are not familiar with the peculiarity of nicotine/cotinine pharmacokinetics in mice, we attempted to estimate the level of nicotine (and e-liquid vapor) exposure used in the discussed study. Since in this study the animals were continuously exposed to nicotine vapor over 90 min and the T1/2 of cotinine in C57BL/6 mice is 37.5 min, the cotinine level (267ng/mL) measured after the termination of nicotine did not reach steady-state (CotSS). Nonetheless, using equation (1) CSS= Ct/(1-exp(-ln(2)/T1/2*t)), CotSS for this study can be calculated as 329 ng/mL. Assuming that the bioavailability of nicotine = 1 and all nicotine is converted to cotinine, CotSS can be calculated using equation (2) CotSS = (Ko nic/CLcot)*R, were Ko nic is the level of nicotine exposure in ng/min, CLcot is the total clearance of cotinine and R is ratio of the molecular weight of cotinine (176) to that of nicotine (162). The general form of equation (2) can be found in Gillette (2012). The ¬¬equation (2) can be rearranged as equation (3) Ko nic, = CotSS * CLcot/R. Using this equation, CotSS=328 ng/mL (see above), CLcot=0.52 mL/min, measured in 25 g C57BL/6 mice (Siu & Tyndale, 2006), R = 1.09, and assuming that the body weight of C57BL/6 mice used in the discussed study was 25g (we were unable to find the body weight in the paper), Ko nic can be calculated as 583 ng/25g/min (2.1 mg/kg/90min). Since animals were exposed to vapor twice per day the daily dose was 4.2 mg/kg nicotine, which corresponds to a daily nicotine exposure dose for a 70 kg human as high as 294 mg/day, which roughly corresponds to smoking 200 cigarettes.

As we stated above, in our calculation two assumptions have been made: 1) the bioavailability of nicotine=1.0; and 2) all nicotine is converted to cotinine. In case the bioavailability is < 1 and/or not all nicotine is converted to cotinine, then in order to reach the measured level of blood cotinine, the level of nicotine exposure would be even higher than the value we calculated.

To support our calculations we also analyzed the data from a published study where C57BL/6 mice received a continuous intravenous nicotine infusion over 10 days (Marks et al., 2004). In this study, using an infusion of nicotine at a rate of 4 mg/kg/h, the observed steady-state level of cotinine was 750 ng/mL. Therefore to obtain the target 267 ng/mL cotinine level reported in the discussed study, the rate of nicotine infusion in these mice would have been 1.76 mg/kg/h (2.64 mg/kg/1.5h). For twice per day exposure the daily dose would be 5.3 mg/kg/day or 370 mg/day for a 70 kg human, more than ten times the nicotine exposure of a typical cigarette smoker.

Taken together our calculations suggest that animals in the discussed study were exposed to nicotine vapor at an intensity which corresponds to a daily exposure in humans on the order of 300-370 mg nicotine. With 1.6% nicotine concentration in e-liquid, to achieve such a dose of nicotine it would be necessary to utilize 18-23 mL e-liquid per day. Using the average value of e-liquid consumption per puff of 0.005mL (Farsalinos et al., 2013) the number of e-cig puffs per day can be calculated as 3600-4600.

It should be noted that in our calculations we postulated that the blood for cotinine measurement was taken immediately after the end of 90 min of exposure. In the results section the authors stated that "Blood was collected … within 1 h of the final exposure" but in the methods section they stated that "exposure was assessed by measuring serum cotinine at 1 h after exposure." If the last statement is correct, because of the fast elimination of cotinine in mice the level of exposure in the study was 3 times higher (2^(60/37.5) ≈ 3) than the above-calculated values. In other words, to obtain the same exposure in humans the e-cig user should take 11000 – 13000 puffs per day. Assuming 8 hours of sleep per day, in order to acquire such a high number of puffs e-cig users would need to take 11-13 puffs per minute and thus practically take an e-cig puff with each breath.

In conclusion we recommend that the results of the discussed study should be interpreted with caution and that more studies with more realistic levels of e-liquid exposure should be conducted.

Sincerely,
Alexey G. Mukhin M.D., Ph.D. and Jed E. Rose, Ph.D.
Center for Smoking Cessation, Duke University Medical Center

References:

Benowitz et al., Handb Exp Pharmacol. 2009; (192):29-60
Farsalinos et al., Int J Environ Res Public Health. 2013; 10(6):2500-14
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In WB Jakoby (Ed.), Enzymatic Basis of Detoxication, Vol. 1, Chapter 2, Academic Press
Marks et al., Neuropharmacology. 2004; 46(8):1141-57
Siu and Tyndale, Mol Pharmacol. 2007; 71(3):826-34

Competing interests declared: AGM: No competing interests to declare.
JER: Consultancy and patent purchase agreement with Philip Morris International.

http://www.plosone.org/annotation/listThread.action?root=85496

Reply

Bernd Mayer says
23. February 2015 at 10:50

The authors raise an excellent point based on much faster metabolism of nicotine in mice than in humans. I was not aware of this species difference but verified it in the literature. Accordingly, comparing cotinine plasma levels of mice and men is an invalid measure for nicotine exposure.

Reply

E-Zigarette-Wissen says
6. March 2015 at 21:36

Thank you very much for this article Dr. Mayer. Since i changed from smoking to vaping, after 12 years of inhaling tobacco, i have never been ill. There was a kind of throat ache i had almost every day, when i was a smoker. It is gone and i can take more then 10 steps, without making a break to breath air. Vaping changed my life.

Reply

yaltis says
9. March 2015 at 4:18

Dear Doctor,
did you notice this?
"Our choice of menthol E-cigs may not be representative of other flavors. Menthol flavored E-cig liquids are moderately cytotoxic compared to other flavors [43], and there is little evidence to suggest that mentholated cigarettes are more or less toxic than other cigarettes. However, menthol suppresses nicotine metabolism [45], and thus may have health impacts that are not observed with other flavors. "

Reply

Ezig Preis says
15. March 2015 at 13:57

Herzlichen Glückwunsch zur Verleihung des Vaping Advocate of the Year 2015.
Vielen Dank für die Unterstützung der Dampfergemeinde.

Dampfende Grüße
Ivonne

Reply

Uri says
19. March 2015 at 13:28

"Nicotine and nicotine replacement drugs seem to attenuate inflammation and enhance proliferation but the effect appears to be marginal."
http://www.ncbi.nlm.nih.gov/pubmed/22566015

However, most importantly, the CPS-I and CPS-II studies failed to find a significant correlation between smokeless tobacco and influenza/pneumonia (see Table 8.6, Harm reduction in nicotine addiction Helping people who can't quit A report by the Tobacco Advisory Group of the Royal College of Physicians, October 2007).

Reply

Joe says
22. March 2015 at 0:14

Endlich mal jemand der sich ein beachtliches Wissen angeeignet hat in einem

Thema in dem das fast unmöglich erscheint. Jemand der " Ich weiss es nicht" sagt wenn er sich nicht sicher ist und somit mehr Intelligenz zu Tage trägt als jemand der aufgrund Halbwahrheiten eine These zusammenwürfelt (so logisch diese auch erscheinen mag, ist es jedoch unverantwortlich). Vielen Dank das Sie soviel von Ihrer wenigen und kostbaren Freizeit geopfert haben um mit Vorurteilen, Panikmache und falscher Werbung aufzuräumen. Das, was Sie für uns Dampfer gemacht haben verdient mehr als nur einen "Vaping Advocates Award"! Selbst wenn die Dampfer-Gegner sich nicht überzeugen lassen, nimmt es mir ein großes Unbehagen da ich nun endlich weiss was das E-Dampfen mit mir macht bzw. kann ich das gesundheitliche Risiko nun sehr viel genauer einschätzen. Was vorher nicht möglich war, da man entweder euphorische Dampfer-Propaganda oder Panikmachende Lügen von beiden Seiten vorgeworfen bekam. Nach 3 Jahren Dampfen endlich ein Lichtblick und Objektivität. Ich wünsche Ihnen nur das Beste.
Liebe Grüße aus Graz
Joe

Reply

Mario says
24. May 2015 at 13:29

Ich möchte mich Joe anschließen. Ich habe mir gerade die Podiumsdiskussion mit Ihnen in Graz auf Youtube angesehen. Vielen Dank für Ihre offenen und klaren Worte und für Ihr Engagement für die E-Zigarette.
Viele Grüße aus München
Mario

Reply

John says
27. June 2016 at 18:43

Still better than tobacco cigarettes...

Reply

Trackbacks

How You Vape. Are you a lung or mouth inhaler? | Vaping Links And More says:
30. May 2015 at 14:19
[...] we go any further, the lung effects with Bernd Mayer are here and with Dr Farsalinos [...]

Reply

Exposed: 18 E-Cig Studies That Are Killing Smokers says:
26. November 2015 at 14:17
[...] Bernd Mayer: Electronic cigarettes and airway infections – Update [...]

Reply

The Week in Vaping – Sunday January 31st, 2016 says:
31. January 2016 at 14:16
[…] and animals to humans is problematic, to say the least. A similar (older) study in mice was well-addressed here by Bernd Mayer, but needless to say, there is very little new or concerning information from this new […]

Reply

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