

Medical rubber anaphylaxis II (submitted to The Lancet, January 26, 2016)

Key words: anaphylaxis, BTT (benzothiazole-thiolate), ethics in medical journalism, IgE allergens, ionic and non-ionic contrast agents, latex allergy, MBT (mercapto-benzothiazole), natural rubber contamination

Latex is promoted as the cause of natural rubber allergy, but a rubber manufacturing catalyst MBT (mercapto-benzothiazole) is much more significant. Although latex is present in medical natural rubber parts, it was MBT leaching and contaminating injected ionic contrast during IVP examinations that caused two clusters of allergic reactions (including anaphylaxis) in a single office practice. MBT combines with plasma proteins creating an IgE protein-hapten allergen. MBT contamination from disposable syringes caused worldwide death of human cells in laboratory cultures (1981). Hammersmith Hospital (Meek and Pettit, Lancet, 1985) found 91 babies with "potentially toxic" MBT blood levels. Peterson and Juhl (FDA), 1985, found 50 per cent of disposable syringe natural rubber leached MBT into syringe contents, the MBT being falsely read immunologically (RIA and HPLC testing) as digoxin; this coincided with an epidemic of increased deaths on a cardiac ward at the Toronto Hospital for Sick Children, falsely attributed to digoxin poisoning by a nurse (Susan Nelles).

The WHO's Drug Monitoring Centre's Uppsala Reports, reviewing a book on the Toronto baby deaths (The Nurses Are Innocent, Dundurn Press, 2011), was disturbed by the difficulty in raising awareness of the persisting MBT hazard, noting it "... reveals the systemic failure of government health protection agencies to protect citizens from a known allergenic and toxic chemical, MBT, a worldwide contaminant of injections for 30 years, with medical journals aiding and abetting the process by refusing to publish informative articles on public health issues related to MBT contamination of injections. A cursory internet search for MBT as an accelerant in the rubber industry shows that it is still widely used: wherever we are, we should be alive to possibilities of unusual anaphylactic reactions/toxic effects."

The letter, below, was submitted to the Lancet as a follow up on a 1990 letter the Lancet published ("Medical rubber anaphylaxis") that warned about worldwide MBT contamination of injections. The following Lancet submission was rejected. The letter and the ensuing correspondence follows.

Medical rubber anaphylaxis II (submitted to the Lancet, January 26, 2016)

MBT (mercapto-benzothiazole), a rubber manufacturing catalyst, is an IgE hapten-protein allergen and a cumulative toxin because of protein binding.¹ MBT from rubber seals of disposable syringes (1983) and ampoules (1987, caused two clusters of ionic radiopaque injection reactions².

MBT, contaminating half of digoxin unit-doses, caused high digoxin in assays; leached MBT reacted immunologically as digoxin (RIA-based

testing), exposing frequency of MBT contamination.³ Concurrently, a nurse was falsely charged with serial murder at the Toronto Hospital for Sick Children, based on high RIA digoxin on babies' autopsies⁴.

A new expensive non-ionic radiographic "dye" substantially reduced severe IVP reactions compared to inexpensive ionics (1985), making non-ionics preferred agents⁵. However, non-ionic dye ampoules were sealed with synthetic (non-MBT, non-latex) rubber, whereas inexpensive ionic contrast ampoules used allergenic MBT-latex-rubber seals.

A Lancet letter suggested eliminating MBT-rubber contact in ionic ampoules manufactured after 1990 might reduce the risk of anaphylactic reactions to ionic injections. F.D.A. statistics confirmed that U.S. severe reactions to ionic and non-ionic radiopaque contrast became as low as non-ionics after 1990.⁶ Surprisingly, this evidence failed to increase usage of inexpensive equally safe ionics.

Despite MBT being a "a worldwide contaminant of injections for 30 years"⁷ - leaching from disposable syringe and ampoule natural rubber - the rubber contact in much pharmaceutical packaging sometimes remains unidentified,⁸ with the Lancet's 1990 warning (reference 2) remaining unheeded worldwide.

- 1 Meek JH, Pettit BR. 1985 *Avoidable accumulation of potentially toxic levels of benzothiazoles in babies receiving intravenous therapy*. Lancet. **2**, 1090-1092
- 2 Hamilton G. 1990 *Medical rubber anaphylaxis*. Lancet. **336**, 1453-1454
- 3 Reepmeyer JJ. 1983 *Contamination of injectable solutions with 2-mercaptobenzothiazole leached from rubber closures*. J. Pharm. Sc. **72**,1302-1305
- 4 Hamilton G. 2011 *The Nurses are Innocent – The Digoxin Poisoning Fallacy*: Chapter 18, Falsely high digoxin readings on autopsy digoxin tests. Dundurn Press, 149-156
- 5 Katayama H, Yamaguchi K, Kozuka T et al. 1985 *Adverse reactions to ionic and nonionic contrast media. A report from the Japanese Committee on the Safety of Contrast Media*. Radiology. **175**, 621-628
- 6 Lasser EC, Lyon GL, Berry CC. 1997 *Reports on contrast media reactions: analysis of data from reports to the U.S. Food and Drug Administration*. Radiology, **203**, 605-610
- 7 Edwards R. 2013 *Lethal, odd and ‘new’ in pharmacovigilance.*, Uppsala Reports (World Health Organization), **61**, 10-11
- 8 Hamilton RG, Brown RH, et al. 2005 *Administering pharmaceuticals to latex-allergic patients from vials containing natural rubber latex closures*. Am. J. Health-Syst.Pharm. **62**, 1822-1827

Rejection and appeal process:

On Mar 15, 2016, at 1:23 PM, The Lancet Peer Review Team wrote:

Manuscript reference number: THELANCET-D-16-00672

Title: Medical rubber anaphylaxis II

Dear Dr. Hamilton,

Thank you for submitting your Letter to The Lancet. Having discussed your Letter with the Editor, and weighing it up against other submissions we have under consideration, I am sorry to say that we are unable to accept it at this time. Please be reassured that your Letter has been carefully read and discussed by the Editors. Thank you for your interest in The Lancet, I hope this decision does not deter you from considering us again in the future.

Yours sincerely

Audrey Ceschia, Senior Editor

Letter of Appeal: March 16, 2016

Dear Editor Ceschia,

I should like to appeal the decision to reject: THELANCET-D-16-00672

Title: Medical rubber anaphylaxis II.

My defence is based on a number of factors, the principal one being that it was carefully written so that there would be no reason to reject it, based on accepted medical practice and ethics. The lack of criticism of the content attests to this.

The WHO's Drug Monitoring Centre in Uppsala, as cited in the article, notes that MBT (mercapto-benzothiazole) contamination of injections (from rubber seals of syringes and ampoules and from three components of I.V. and blood transfusion administration sets) has been allowed to continue for 30 years (it was really first revealed in 1969). As noted in my 1990 Lancet article, it was (then and still is now) most prevalent in India, China and other Eastern countries, where natural rubber is used widely. This is certainly worthy of being revealed to the medical community by The Lancet.

In 1983, a cluster of allergic reactions to contrast medium injections in my office was traced to natural rubber components of BD disposable syringes. Health Canada's Bureau of Medical Devices in Ottawa withheld the specific name of the chemical contamination, informing me that it was "a phenolic compound." In spite of this extremely generic term for the contamination, the CMAJ decided to publish a report on this contamination.

Dr. Harry Fisher, the editor in charge of contrast medium articles at Radiology, asked me to write a similar letter for Radiology. The letter was then rejected by other members of Radiology's editorial board. I then confronted the Bureau of Medical Devices, demanding a specific identification of "a phenolic compound." That chemical was MBT. I contacted Dr. Fisher with this information, who then asked me to add this specific information and send the submission to him personally. The article was published in 1984, accompanied by Dr. Fisher's commentary. I substituted rubber-free Danish syringes for all my injections thereafter.

After encountering another cluster of allergic reactions in 1987, again with anaphylaxis, it was the natural rubber seals of contrast ampoules that caused MBT injection contamination. This resulted in another publication in the CMAJ in 1987. My MBT articles caught the attention of the Ontario Medical Review editorial board, which asked me to write an article on MBT contamination of injections. The requested article was submitted, revised in accordance with editorial amendments and I accepted the galley proofs of the amended submission (as was the way in 1988). In two days, Editor David Fletcher informed me by phone that the article would not be published, because of a threat of being sued.

So, there is a pattern behind the prevention of the publication of articles alerting the practising medical community of the known persistent hazard of contamination of injections by MBT, a chemical which, because it becomes bound to plasma proteins, becomes both an IgE-mediated allergen – and a cumulative toxin (as noted in my article, citing another Lancet article by Meek and Pettit). It certainly would capture the attention of the general public who are unacceptably exposed to MBT contamination.

Letters generally have a lower threshold for editorial scrutiny than articles. "Medical rubber anaphylaxis" (Lancet 1990) was accepted by return mail, with the only editorial change being

the substitution of “worldwide” for “global.” I expected a similar response this time, because of the significance and specificity of the content.

My only request in the selection of an appeal reviewer, is that it be one with an interest in medical ethics as well as an interest in internal medicine.

Sincerely,

Gavin Hamilton

Lancet letter rejecting the appeal, April 15, 2016

Corresponding author: Dr. Gavin Hamilton

Article title: Medical rubber anaphylaxis II

Manuscript number: THELANCET-D-16-00672

Dear Dr. Hamilton,

Thank you for your email and for providing the editors with an opportunity to reconsider your manuscript entitled Medical rubber anaphylaxis II.

However, it is with regret that our decision remains that this paper is not a priority for The Lancet's general readership.

Kind regards, The Lancet