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### Article

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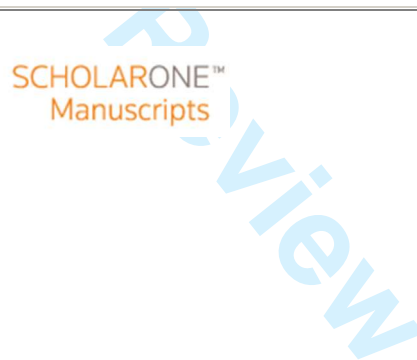
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## Is nitrogen mustard contamination responsible for the reported MT-45 toxicity?

Jason Wallach, Hamilton Morris and Simon D. Brandt

Helander *et al.* are commended for disseminating their case reports in the recent publication entitled "Acute skin and hair symptoms followed by severe, delayed eye complications in subjects using the synthetic opioid MT-45".<sup>1</sup> We have followed reports of side effects associated with MT-45 use for several years and the above publication serves as an important reminder of the risks of harm involved in the unregulated use of new psychoactive substances.

As pointed out in the report the symptoms described in these case reports are reminiscent of chemotherapeutic agents.<sup>1</sup> The authors reported that anticancer drugs could not be detected, thus, excluding their involvement in the reported clinical features.<sup>1</sup> We wish to point out that a number of published synthetic routes to MT-45 describe the use of *N,N*-bis(2-chloroethyl)cyclohexylamine (**1**) as an alkylating agent in the final step of the synthesis.<sup>2-5</sup> An alternate route using *N,N*-bis(2-chloroethyl)-1,2-diphenylethylamine (**2**) (Fig. 1) as the alkylating intermediate has also been reported.<sup>2-4</sup> These reagents are nitrogen mustards and it's conceivable that other synthetic routes might employ different mustard intermediates at various stages as well. Such agents would likely be missed in analysis as they are not employed as anticancer drugs or commonly encountered. Metabolic transformation of nitrogen mustard contaminants could further complicate their detection in a clinical setting.

Nitrogen mustards are reactive alkylating agents with recognized uses in chemotherapy<sup>5</sup> but also chemical warfare<sup>6</sup>, and they are known to cause many of the same adverse effects associated with use of MT-45.<sup>5</sup> The reagents employed in MT-45 synthesis (**1**, **2**) and/or partially reacted side products (for example structures **3-4** in Figure 1) might also act as an alkylating agent due to their electrophilic nature and this raises the question as to whether the symptoms described by Helander *et al.*<sup>1</sup> as well as those described on drug discussion forums could reflect the presence of ill-purified batches of MT-45. Poisoning with nitrogen mustards could have long lasting consequences for the user, including carcinogenesis.

It should not be excluded that MT-45 was the sole agent responsible for the reported symptoms and the authors propose several potential leads. However the search for contaminants associated with MT-45 synthesis might also be worthy of investigation. Conclusive evidence will require detection of contaminated MT-45 samples along with follow-up studies in animal models. Our own analysis of a single sample of MT-45 from an online vendor obtained in January 2015 did not appear to contain any major organic impurities but as different distributors likely obtain this substance from distinct sources or manufacturers, it seems possible only some batches would be contaminated. The analysis of blood samples for the presence of

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3 the alkylating agents and some potential bio-marker metabolites comparable to  
4 those seen with related nitrogen mustards<sup>8</sup> might also be worthy of investigation.  
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## 8 References

- 9  
10  
11 1. Helander A, Bradley M, Hasselblad A et al. Acute skin and hair symptoms  
12 followed by severe, delayed eye complications in subjects using the synthetic  
13 opioid MT-45. *Br J Dermatol* 2016.  
14  
15 2. Natsuka K, Nakamura H, Uno H et al. 1-Substituted 4-(1, 2-diphenylethyl)  
16 piperazine derivatives and their analgesic activities. 1. *J Med Chem* 1975; 18:  
17 1240-44.  
18  
19 3. Natsuka K, Nakamura H, Negoro T et al. Studies on 1-substituted 4-(1, 2-  
20 diphenylethyl) piperazine derivatives and their analgesic activities. 2.  
21 Structure-activity relationships of 1-cycloalkyl-4-(1, 2-diphenylethyl)  
22 piperazines. *J Med Chem* 1978; 21: 1265-69.  
23  
24 4. Nishimura H, Uno H, Natsuka K et al. 1-Substituted-4-(1, 2-diphenylethyl)  
25 piperazine derivatives and compositions containing the same. U.S. Patent No.  
26 4,080,453. 1978.  
27  
28 5. European Monitoring Centre for Drugs and Drug Addiction (EMCDDA). MT-  
29 45. Report on the risk assessment of MT-45 in the framework of the Council  
30 Decision on new psychoactive substances. Lisbon, Portugal. Available at:  
31 [http://www.emcdda.europa.eu/attachements.cfm/att\\_233323\\_EN\\_MT-](http://www.emcdda.europa.eu/attachements.cfm/att_233323_EN_MT-45%20Risk%20Assessment%20Report.pdf)  
32 [45%20Risk%20Assessment%20Report.pdf](http://www.emcdda.europa.eu/attachements.cfm/att_233323_EN_MT-45%20Risk%20Assessment%20Report.pdf) (last accessed: 31.12.2016)  
33  
34 6. Livingstone E, Zimmer L, Leister L, Schadendorf D. Alkylating agents. In:  
35 *Dermatologic Principles and Practice in Oncology: Conditions of the Skin, Hair,*  
36 *and Nails in Cancer Patients*, First Edition. Edited by Mario E. Lacouture.  
37 2014 John Wiley & Sons, Inc. Published 2014 by John Wiley & Sons, Inc. 2014;  
38 147-159.  
39  
40 7. Chauhan S, Chauhan S, D'Cruz R, Farugi S et al. Chemical warfare  
41 agents. *Environ Toxicol Pharmacol* 2008; 26: 113-122.  
42  
43 8. Black RM. An overview of biological markers of exposure to chemical warfare  
44 agents. *J Anal Toxicol* 2008; 32: 2-9.  
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Figure 1. Mustard intermediates used in the synthesis of MT-45 and possible alkylating agent side products.

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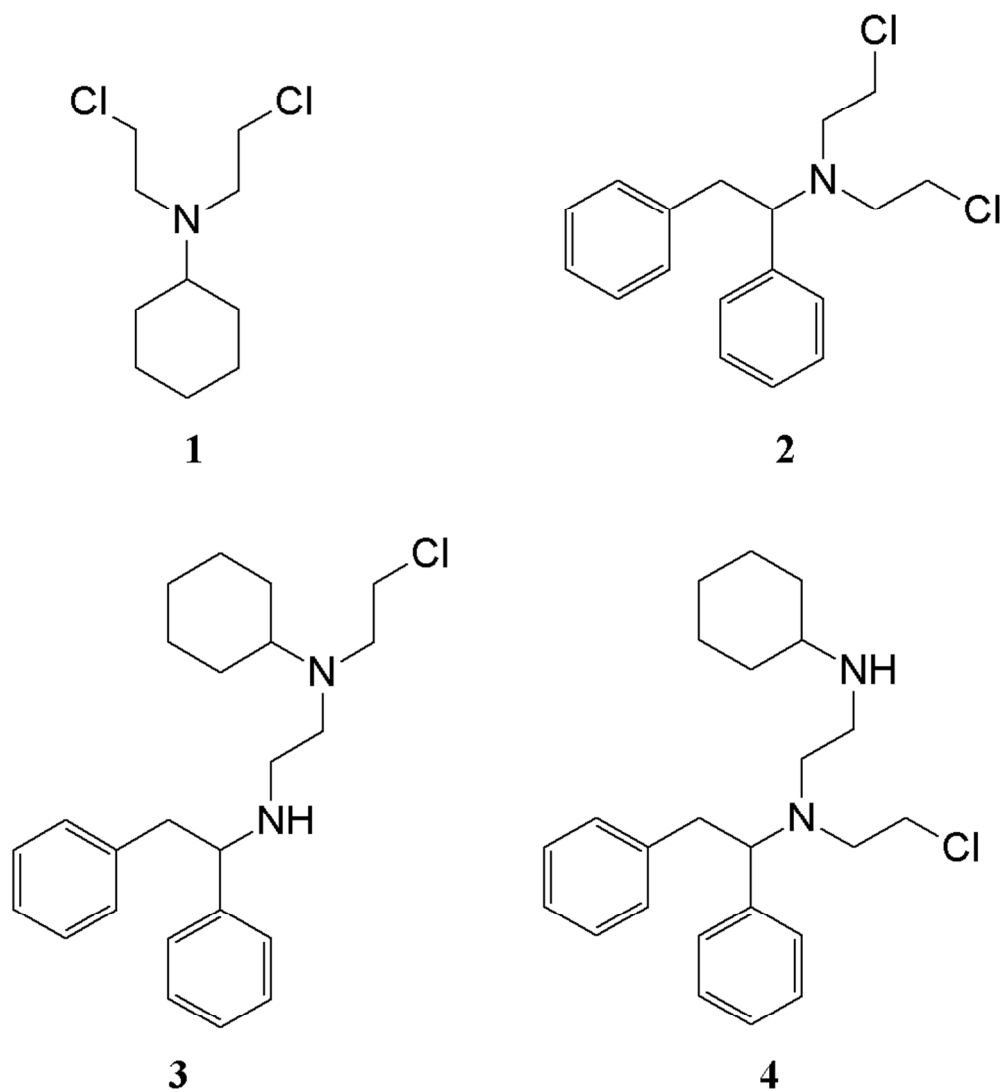


Figure 1. Mustard intermediates used in the synthesis of MT-45 and possible alkylating agent side products.

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