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BY ELECTRONIC DELIVERY

Division of Dockets Management
Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, Maryland 20852

Re: Citizen Petition (Docket Number: FDA-2022-P-0509)

Please find attached three references, which discuss the formation of the potentially genotoxic aziridine impurity during amphetamine synthesis, submitted in support of the arguments in our Citizen Petition (Docket Number: FDA-2022-P-0509), submitted on March 31, 2022. Also enclosed is a summary of the attachments, including specific references to the pages of importance. We ask that FDA consider these publications during its review of our Citizen Petition. Please contact us if you have any questions.

Respectfully Submitted,

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SUMMARY OF ATTACHMENTS

Attachment A. Aalberg, L., Andersson, K., Bertler, C., Boren, H., Cole, M.D., Dahlen, J., Finnon, Y., Huizer, H., Jalava, K., Kaa, E., Lock, E., Lopes, A., Poortman-van der Meer, A., Sippola, E. "Development of a harmonized method for the profiling of amphetamines I. Synthesis of standards and compilation of analytical data" *Forensic Science International* 2005, *149,* 219-229.

Reference material was synthesized for substances that are frequently present as synthetic impurities for at least one of the three approaches most often used to illicitly synthesize amphetamine, namely, the Leuckart, the reductive amination of benzyl methyl ketone and the nitrostyrene routes.

In Table 1 on page 221, 2-methyl-3-phenylaziridine is listed as a known impurity from the nitrostyrene route. Its synthesis is described on page 224.

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Attachment B. Andersson, K., Jalava, K., Lock, E., Finnon, Y., Huizer, H., Kaa, E., Lopes, A., Poortman-van der Meer, A., Cole, M.D., Dahlen, J., Sippola, E. "Development of a harmonized method for the profiling of amphetamines III. Development of the gas chromatographic method" *Forensic Science International* 2007, *169,* 50–63.

This paper describes the development of gas chromatographic methods to detect forensic impurities in syntheses of amphetamine and methamphetamine. Specifically, in Table 6 on page 55, the paper describes 2-methyl-3-phenylaziridine, compound 22 in the table, as an impurity identified in amphetamine synthesized by the Leuckart, reductive amination and nitrostyrene methods.

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Attachment C. Barker, W.D., Antia, U. "A study of the use of Ephedra in the manufacture of methamphetamine" *Forensic Science International* 2007, *169,* 102-109.

In this paper, the main alkaloids obtained from the Ephedra plant have been reduced using four common methods used by the clandestine operator. The intermediates and byproducts of these reductions have been identified and/or tentatively assigned and the mechanism of formation discussed.

On page 104, the red phosphorous/iodine reduction of norephedrine to amphetamine is discussed. As shown in Figure 3 and discussed further in the right hand column on page 104, the cis/trans mixture of 2-methyl-3-phenylaziridine is detected.

Furthermore, on page 106, the authors discuss the metal catalyzed hydrogenation of norephedrine, via its chlorointermediate. They describe the presence of the cis/trans mixture of 2-methyl-3-phenylaziridine and provide a GCMS chromatogram in Figure 9 on the top of page 107 for this aziridine mixture. Also, Table 1 on the top of page 108 provides a summary of products, byproducts and intermediates produced on the reduction of Ephedra derived alkaloids. *Cis/trans*-2-methyl-3-phenylaziridine is listed as an intermediate in the reaction sequence starting from Norephedrine/Norpseudoephedrine in the second and fourth line.