Nicotine has been studied extensively because of its presence in tobacco products. Due to its chronicity, nicotine can exist in two chiral enantiomeric forms; however, the tobacco plant produces predominantly (S)-nicotine with only a trace of (R)-nicotine. Consequently, consumers of tobacco products have been exposed to rather small amounts of (R)-nicotine over the years. 

Recently, synthetic nicotine has become commercially available and can be supplied as a United States Pharmacopeia (USP) grade (S)-nicotine, or a 50/50 (R)/(S) mixture, or as a mixture in varying ratios of (S)/(R) enantiomers. Synthetic (S)-nicotine can be obtained by asymmetric synthesis or by racemic synthesis followed by classical resolution using diastereomeric salts. The primary objective of this study was to determine the amount of (R)-nicotine in commercial sources of tobacco-derived USP nicotine, synthetic nicotine, and e-liquids used in Electronic Nicti Delivery Systems (ENDS). A secondary objective was to examine the literature on the pharmacology of (R)-nicotine considering the potential exposure to tobacco consumers. Nicotine samples were analyzed by chiral GC-MS and chiral HPLC-UV. The analysis of four lots of tobacco-derived USP nicotine revealed only a small amount of (R)-nicotine, whereas one sample of synthetic nicotine was found to contain a 50/50 mixture of enantiomers. Analysis of two lots of e-liquids used in ENDS indicated that each contained a 50/50 mixture of (R)- and (S)-nicotine and was synthetic. In this study, large amounts (50%) of (R)-nicotine were found in some commercial nicotine sources. Consequently, tobacco consumers may be subject to higher nicotine exposure levels than in the past. A literature review indicated that with some exceptions (R- and (S)-nicotine were found to exhibit a similar pharmacological profile, with (R)-nicotine being often not, but not always, pharmacologically active than (S)-nicotine.

Nicotine is typically obtained from the tobacco plant (Nicotiana tabacum, Nicotiana rustica, etc.) by extraction and purification by vacuum distillation. The enantiomeric form of (S)-(−)-nicotine (S)-nicotine or (R)-(+)
icotine, with a small amount of (−)2-5.0% of (R)+nicotine. The structures of (S)-nicotine and (R)-nicotine are shown in Figure 1. Synthetic (S)-nicotine can be obtained by a variety of asymmetric synthesis methods. Synthetic (S)-nicotine can also be obtained by racemic synthesis followed by classical resolution using diastereomeric salts. However, synthetic nicotine may contain traces of related substances such as starting materials and residual solvents.

Nicotine is a common component of the e-liquids used in ENDS. The source of nicotine that has been found in the e-liquids can be tobacco-derived nicotine (50 to 99.2%) or synthetic nicotine (5 to 50%). As an enantiomer of nicotine, this nicotine is found in commercially available nicotine samples and e-liquids was determined by both chiral methods. A summary of nicotine in some commercial nicotine sources and in the nicotine of two ENDS e-liquids is shown in Table 1. Consequently, depending upon product selection, consumers using ENDS with e-liquids prepared with synthetic nicotine may be exposed to higher levels of (R)-nicotine compared to combustible cigarettes and oral tobacco products which contain the naturally occurring (S)-enantiomer. With some exceptions, (R)- and (S)-nicotine exhibit a similar pharmacological profile, with (R)-nicotine being often not but not always pharmacologically active than (S)-nicotine. Synthetic nicotine composed of large proportions of (R)-nicotine may not, and in of itself, pose a pharmacological safety issue, though impurities resulting from the synthesis process may complicate the issue.