Prevalence of smoking among opioid-dependent individuals is four-fold that of the general US adult population and is associated with increased risk for smoking-related morbidity and mortality. The 2009 passage of the Family Smoking Prevention and Tobacco Control Act gave the FDA regulatory jurisdiction over tobacco products, and a public policy mandating a reduction in cigarette nicotine content is currently being considered. Such a policy could dramatically reduce smoking rates and smoking-related adverse health effects in the general population. Unfortunately, little is known scientifically about the effects of reduced-nicotine cigarettes in populations that are especially vulnerable to smoking and adverse health outcomes, including smokers with comorbid other drug dependence. Whether this more dependent group might respond with compensatory increases in smoking rate or inhalation patterns, potentially increasing exposure and adverse health effects, is unknown. The overarching objective of this project is to conduct a thorough experimental evaluation of the abuse liability and health effects of very low nicotine content (VLNC) cigarettes in opioid-dependent smokers. We will compare cigarettes varying in nicotine content across a range of doses starting from levels approximating those in usual brand cigarettes to very low nicotine levels (0.83, 0.28, 0.10, 0.03mg) using brief- and extended-exposure protocols. This project will represent the first investigation of VLNC cigarettes in smokers with opioid dependence or other substance use disorders and stands to contribute new scientific knowledge with the potential to inform FDA policy decisions. As Primary Aims, we will evaluate whether VLNC substitute for usual-nicotine cigarettes during brief exposure, without producing compensatory increases in smoking, and we will compare VLNC and usual-nicotine cigarettes, under conditions of extended (12-week) exposure, on smoking rates, toxin exposure levels, and nicotine dependence. As Secondary Aims, we will assess adherence, withdrawal, and cigarette demand, biomarkers of exposure to carcinogens, markers of pulmonary, cardiovascular and neurocognitive function and use of other non-prescribed drugs. Understanding how opioid-dependent smokers respond to reduced-nicotine cigarettes is essential for evaluating the potential impact of a nicotine reduction policy. We propose to provide the first experimental analysis of the effects of VLNC cigarettes in opioid-dependent smokers using measures that are relevant to the abuse liability and potential health impact of these products. Taken together, these data have the potential to directly inform FDA policy decisions regarding reduced-nicotine tobacco products.