**August 13, 2015**

**POINT BY POINT RESPONSE TO "*USING EVIDENCE TO TALK ABOUT CANNABIS*"** a report published by the International Centre for Science in Drug Policy, 30 Bond St.,Toronto, ON M5B 1W8

**BOTTOM LINE: "A lifetime of cannabis use carries a low risk of dependence (9%)."**

Rebuttal: As reviewed by Nora Volkow (Director of NIDA) in the same New England Journal of Medicine publication the authors cite (page 7 of their report), when use begins in the teenage years, the overall risk of dependence is **17%**, and for those who progress to daily use, the risk of dependence is as high as **50%**.

David Nutt is the senior pharmacologist on the board of the International Centre for Science in Drug Policy (ICSDP). **In 2009, he was fired from his position as chief drug advisor for the British government after arguing that ecstasy and LSD were less dangerous than alcohol:**
http://www.theguardian.com/politics/2009/oct/30/drugs-adviser-david-nutt-sacked

As far back as 2004, he had been proposing that benzodiazepine addiction was also not a serious risk after several months of use. In a May presentation of that year entitled 'The Development of New Benzodiazepine (BDZ) and Other Sedative-Anxiolytic-Hypnotic (SAH) Guidelines Suitable for Use by General Adult Psychiatrists', http://www.smmgp.org.uk/download/others/other039.pdf he emphasized that benzodiazepine withdrawal reactions take a long time to develop:
"4 weeks: very low risk
4 months: 5–10%
2 years: 25–45%
6–8 years: 75%"

This presentation of his occurred during a general time period when he was funded by several pharmaceutical companies. According to the U.K. Medical Research Council website for 2008 Nutt has the following major declarations of interest:
Personal Remuneration (employment, pensions, consultancies, directorships, honoraria etc)
Consultancies/Advisory Boards – Pfizer, GSK, Novartis, Organon, Cypress, Lilly, Janssen, Lundbeck, BMA, Astra-Zeneca, Servier, Hythiam, Sepracor
Speaking Honoraria – Wyeth, Reckitt-Benkiser, Cephalon
Grants or clinical trial payments – MSD, GSK, Novartis, Servier, Janssen, Lundbeck, Pfizer, Wyeth, Organon.

Meanwhile, many other reputable scientists have issued reports on the addictive power of benzodiazepines and the dangers of withdrawal, as described in this recent blog:
http://www.huffingtonpost.com/van-winkles/is-it-bedtime-for-benzos_b_7663456.html

**Re: Increases in potency**

"Concerns over increases in cannabis potency are rooted in the assumption that higher levels of THC are harmful to health. However, the harms of increased cannabis potency are not yet fully understood by scientists. Perhaps counterintuitively, some research suggests that higher cannabis potency may actually lead to a reduction in health harms (especially related to smoking), as consumers might reduce the volume they consume (Van der Pol et al., 2014)."

Rebuttal: Here the authors misstate the conclusions of the cited reference and expose a logical fallacy in their later claim that smoking cannabis is irrelevant to cancer and lung health. The Van der Pol et al. references actually states " Thus, users of more potent cannabis are generally exposed to more delta-9-tetrahydrocannabinol." So whatever benefit may be gained by inhaling less smoke, would be offset by the negative impacts of more THC. At least the ICSDP seems to acknowledge in this section that there is reason for concern in regards to smoking more of this product.

"Importantly, under prohibition, illegal cannabis markets face zero quality control requirements. A strict, legally regulated market for cannabis would put the regulation of THC levels in the hands of governments and public health officials, not criminal entrepreneurs. In the case that cannabis potency is found to be associated with greater health harms, the regulation of cannabis markets by governments becomes even more vital."

Rebuttal: The State of Colorado has done nothing to lower concentration of THC in the products for sale in their state. The sale of extracts makes the home production of concentrated edibles or smoked products very easy.

**Bottom Line: "Evidence to date does not support the claim that cannabis use causes subsequent use of "harder" drugs."**

Rebuttal: There are studies that show such a gateway effect and some that don't. Meanwhile, while this question is being exhaustively investigated, marijuana is doing enough harm all by itself.

**Bottom Line: "There is little evidence to suggest that cannabis use can cause lethal damage to the heart, nor is there clear evidence of an association between cannabis use and cancer."**

Rebuttal: It is agreed that the evidence linking marijuana smoking to cancer is equivocal at this point, but there is strong evidence supporting serious cardiac effects.

The American Heart Association published an editorial in 2008 (Gaziano, 2007, in J Am Heart Assoc) stating among other points that : "a longitudinal follow-up of participants from this study raises concern that regular marijuana use appears to increase one's chance of dying in the period after having an MI (myocardial infaraction)……" And "**these findings should cause state regulators to exercise caution before considering use of marijuana for therapeutic purposes**".

A more recent review published by the American Heart Association (Jouanjus et al., 2014, Cannabis Use: Signal of Increasing Risk of Serious Cardiovascular Disorders, J Am Heart Assoc, 2014;3:e000638 doi: 10.1161/JAHA.113.000638), states in their conclusions: "Increased reporting of cardiovascular complications related to cannabis and their extreme seriousness (**with a death rate of 25.6%**) indicate cannabis as a possible risk factor for cardiovascular

disease in young adults, in line with previous findings. Given that cannabis is perceived to be harmless by the general public and that legalization of its use is debated, data concerning its danger must be widely disseminated. Practitioners should be aware that cannabis may be a potential triggering factor for cardiovascular complications in young people." David Nutt and his colleagues at ICSDP dismiss these concerns as not showing causality, yet one of the frequent physical complaints from users of high strength marijuana is a racing heart, and this from reports where users are posting their experiences asking for advice from other users (e.g. http://www.bluelight.org/vb/archive/index.php/t-199620.html). There are many, many more posts such as this.To dismiss the user's perception that the marijuana triggered their racing heart would be patronizing, at best, especially given the clinical reports of an association.

**Bottom Line: "There is little evidence suggesting that cannabis use is associated with declines in IQ".**

AND

**Bottom line: "While the evidence suggests that cannabis use (particularly among youth) likely impacts cognitive function, the evidence to date remains inconsistent regarding the severity, persistence, and reversibility of these cognitive effects".**

Rebuttal: The evidence is building at this time, but not yet definitive as to the risk of the effect for the average person. And meanwhile, the authors of this report are willing to take the chance that these effects might be severe, persistent and irreversible for any young person in any country?

**Bottom Line: "While scientific evidence supports an association between cannabis use and schizophrenia, a causal relationship has not been established."**

Rebuttal: According to the leading psychiatric epidemiologist in the world (Dr. Robin Murray, who has been knighted in England for his work), causation has been established (as also presented in DiForti et al., in Lancet Psychiatry, 2015): "there is convincing evidence that heavy use of cannabis, especially the high-potency types, increases the risk of schizophrenia up to 5-fold":

http://www.psychiatrictimes.com/specialreports/marijuanaandmadnessclinicalimplicationsincreasedavailabilityandpotency/page/0/2

Also, David Nutt and his colleagues neglected to cite the letter to the editor published on PubMed in conjunction with the Proal et al. paper. The letter revealed the conclusions to be statistically unsupported and in fact, to the extent that there was a trend, the data suggested a trend for increased risk of psychosis even in marijuana users without a family history of psychosis.

Here is the response to the 'proof of causation' question from another pharmacologist's perspective:

1) **Dose-response correlation**, heavier use, more potent products increase the risk (Zammit et al., in *British Medical Jl*, 2002; van Os et al., in *Am J Epidem*, 2002; DiForti et al., in *British J Psychiatry*, 2009; DiForti et al., in *Lancet Psychiatry*, 2015).

2) **Timing**: marijuana use generally precedes the psychosis, in prospective studies of teens (Arseneault et al., in British Med Journal, 2002; Henquet et al., in British Med Journal, 2005; Kuepper et al., in British Med Journal, 2011).

3) **Individuals with schizophrenia who were marijuana users have an earlier age of onset**
(Veen et al., in Am J Psychiatry, 2004; Barnes et al., in British J Psychiatry, 2006; Large et al., in Acta Psychiatr Scand, 2011; De Hert et al., in Schizophr Res, 2011)

4) **Marijuana's active ingredient (THC) elicits psychotic symptoms in the clinical subjects** (D'Souza et al., in Neuropsychopharmacology, 2004; Morrison et al., in Neuropsychopharmacology, 2011; Bhattacharyya et al., in Arch Gen Psychiatry, 2011; Freeman et al., in Schizophrenia Bulletin, 2014)

5) **Users of other potent recreational drugs develop chronic psychosis less often**, e.g. for PCP users, it's about half the rate of marijuana users (Niemi-Pynttari et al., in J Clin Psychiatry, 2013).

6) **Rather than 'self-medicating', marijuana users with psychosis will often quit** to avoid the symptoms, (Fergusson et al., in Addiction, 2005). *But for some, it's too late*.

To conclude, marijuana has been shown to trigger psychosis under controlled clinical conditions and is associated with a chronic psychotic conditions in numerous clinical studies. If this was a carcinogen present in processed food, shown to elicit cancerous changes in clinical studies of animals and associated with cancer in large epidemiological studies with a 2 to 5-fold effect size as seen with marijuana and schizophrenia, it would be removed from the market, even before the exact mechanism (and therefore, absolute proof of causation) was determined.

**Bottom Line: "Evidence suggests that the supply of illegal cannabis has increased under prohibition."**

Rebuttal: But neither has it diminished significantly under legalization in Colorado (http://denver.cbslocal.com/2015/05/06/pot-delivery-services-thriving-in-colorados-black-market/ and http://gazette.com/special-report-clearing-the-haze-black-market-is-thriving-in-colorado/article/1548305

As long as marijuana is taxed at all, the black market will remain just like there is one for cigarettes (http://www.wsj.com/articles/SB10400938577857473793). It is said that the black market for cigarettes is larger than the legal market (http://www.organized-crime.de/KlausvonLampeManuscriptTheIllegalCigaretteTrade2011.pdf). Taxing will remain essential to funding addiction treatment and other social consequences of marijuana use.

In the U.S., the fight against the marijuana supply has definitely been more difficult than in other countries because we have shared a long border with a drug producing country (Mexico). Further worsening of the situation occurred after NAFTA was implemented, allowing large commercial vehicles to cross our borders.

***"Mexico remains the primary foreign source of marijuana and methamphetamine destined for U.S.markets and is also a source and transit country for heroin. ONDCP 2013 report: Office of National Drug Control Policy, NATIONAL SOUTHWEST BORDER COUNTERNARCOTICS STRATEGY"***

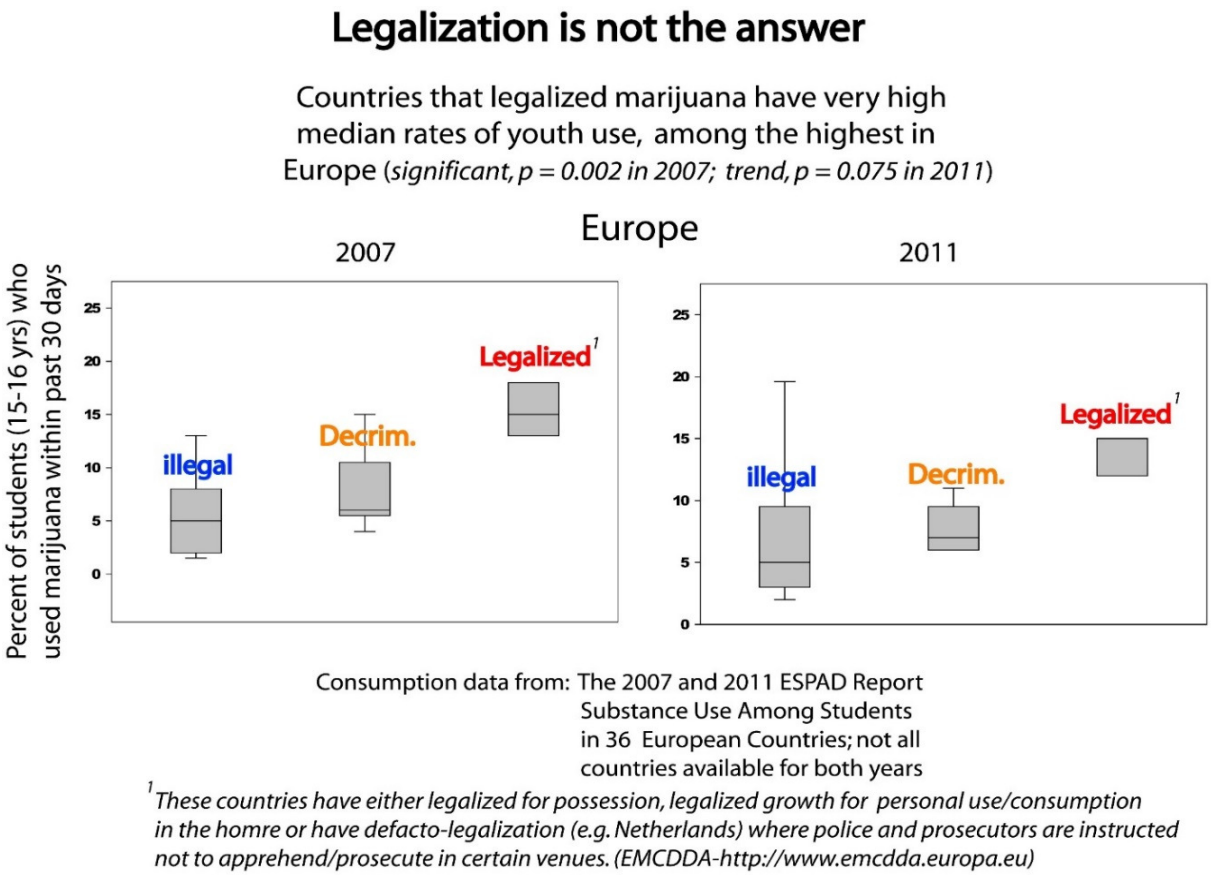
***Drugs Cross Border By Truck, Free Trade And Chance***
***Http://www.npr.org/templates/story/story.php?storyId=131106638***

***NAFTA And The Drug Cartels: "A Deal Made In Narco Heaven", Ryan Grim, Huffington Post http://www.huffingtonpost.com/ryan-grim/nafta-and-the-drug-cartel_b_223705.html***

To conclude, using the US as an example, although they've had a bigger battle to fight, to say that the fight didn't make a difference is unwarranted.

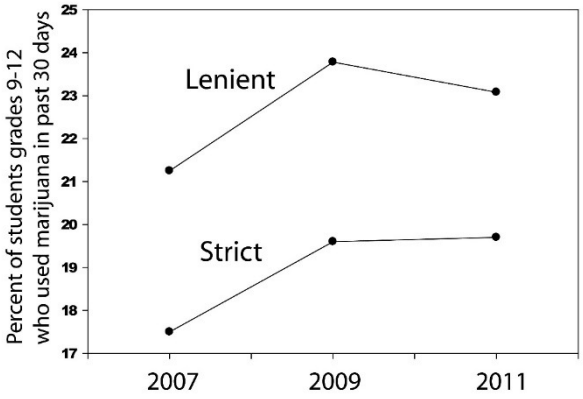
**Bottom line: "Evidence suggests that the policy environment (specifically legal status and enforcement policy) has at most a marginal impact on the prevalence of drug use, thereby suggesting that regulating cannabis markets will not inevitably cause higher levels of cannabis use"** At the same time, a large 15-year research study found that the presence of medical marijuana systems has not led to increases in recreational adolescent cannabis use in the United States (Hasin et al., 2015).

Rebuttal: The quote about medical marijuana not being associated with increases in recreational adolescent cannabis use in the U.S. is incorrect. The same paper they cite found a 27% higher level of use in medical marijuana states, but what the authors were unable to do was tie that difference precisely to the enactment of the laws. The authors should have conducted a time series analysis as it was widely perceived in Colorado that use in teens increased after the dispensaries became more prevalent (well after the law was enacted) based on the prevalence of medical marijuana product in the hands of teens (Salomonsen-Sautel S, S et al., 2012, in (J Am Acad Child Adolesc Psychiatry) and conversely, there may also have been some anticipation of the law as numerous studies show that perception of harm drives their use downward (http://www.monitoringthefuture.org/pubs/monographs/mtf-overview2012.pdf).. Many teens undoubtedly equate medical use to a lower degree of harm.In addition, legalization and de-facto legalization lead to even greater increases in use among teens, young adults and all adults. RAND projects a 54% increase in use if Vermont legalizes (http://www.rand.org/pubs/research_reports/RR864.html). Data already available from Europe, Colorado and the one decriminalized state for which CDC data was collected before and after, more than support those projected trends:



## How Decriminalization is Structured Makes a Difference

States with lenient decriminalization laws have higher rates of youth use*
than states where decriminalization is structured to discourage use (p=0.004)



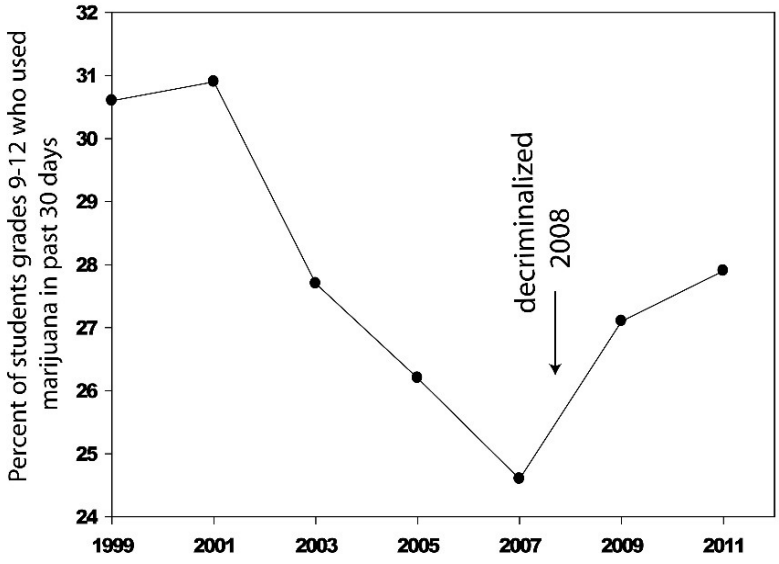

Lenient = no graduated penalties for repeat offenders, no drug education requirement, no community service.

Strict= no jail time for 1st offense but may be a misdemeanor that can be removed from record; or graduated penalties for repeat offenders that may eventually involve jail time and criminal charges; or may have a clause that makes1st offense more serious: in public view (NY) or in auto passenger compartment (MS).

*Data on youth use derived from:
CDC Morbidity and Mortality Weekly Report, Youth Risk Behavior Surveillance - United States, 2007,2009, 2011. Data for 2013 due out in June, 2014. CA and OR (lenient decrim) did not submit data to the CDC.*

| | 2007 | 2009 | 2011 |
|---|---|---|---|
| Lenient decrim laws | AK, CO, ME | AK, CO, ME, MA | AK, CO, ME, MA |
| Strict decrim laws | NC, OH, NE NY, MS, NV | NC, OH, NE NY, MS, NV | NC, OH, NE NY, MS, NV |

## Massachusetts

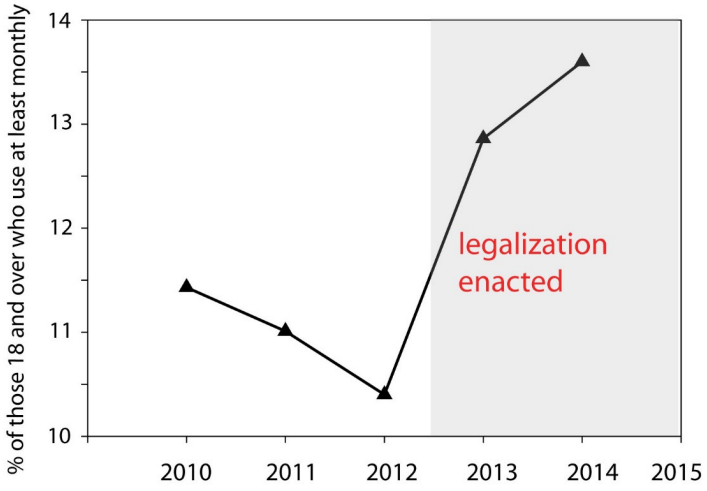



**Massachusetts decriminalization code**: 1 oz (~30 g) or less is a civil fine of $100.
*No increase in penalty for repeat offenses, no requirement for drug education or treatment, no stipulation about carrying in passenger compartment of auto.*

# The effect of enacting a lenient decriminalization code in MA

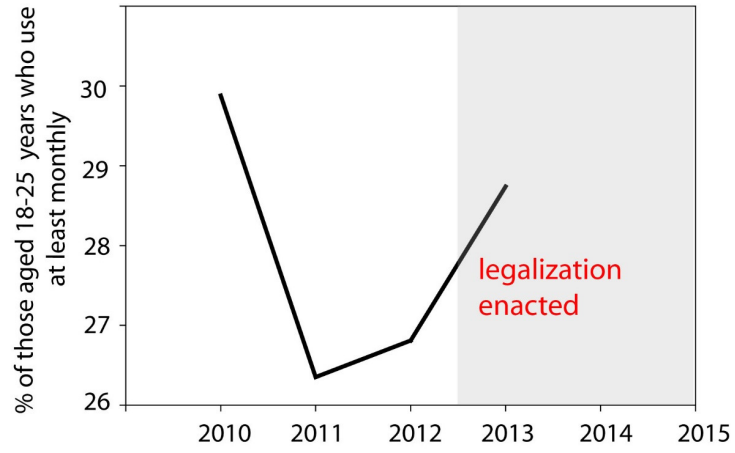
*(the only state where CDC data was available for at least 2 years prior and 2 years post)*

The impact of legalization on past month marijuana use in the State of Colorado
for those aged 18 years and older




*Data source: 2010-2013 NSDUH reports, www.SAMHSA.gov*
*2014: State of Colorado, Behavioral Factor Risk Surveillance Survey*

The impact of legalization on past month marijuana use in the State of Colorado
or those aged 18 to 25




*Data source: 2010-2013 NSDUH reports, www.SAMHSA.gov*

**Bottom line: "While experimental studies suggest that cannabis intoxication reduces motor skills and likely increases the risk of motor vehicle collisions, there is not sufficient data to suggest that cannabis regulation would increase impaired driving and thereby traffic fatalities."**

Here are some reasons to be concerned. THC impairment is a more common finding in "at fault" crashes than in not at fault crashes: http://www.ncbi.nlm.nih.gov/pubmed/14693897 Young adult men are more likely to drive while stoned than while drunk http://consumer.healthday.com/general-health-information-16/misc-alcohol-news-13/college-guys-more-likely-to-drive-while-stoned-than-drunk-study-finds-687780.html, and it took many decades of hard work by MADD and other organizations to make them less likely to drive while drunk. A recent NIDA report shows that cannabis impairment can be serious, and additive with alcohol:http://www.ncbi.nlm.nih.gov/pubmed/26144593,

Traffic fatalities were at a decade-long low in Colorado in 2010, continuing into 2011. Since legalization, fatalities have started to climb and now in the first 6 months of 2015, are 56% higher than the first 6 months of 2010: https://www.codot.gov/library/traffic/safety-crash-data/fatal-crash-data-city-county/Colorado_Historical_Fatalities_Graphs.pdf/view

**Bottom Line: "There is a great deal of uncertainty regarding cannabis regulation and so-called "drug tourism" and it is likely that such activities will vary across different jurisdictions based on the use of different regulatory controls".**

As the authors themselves have pointed out, if uniformly legalized world-wide drug tourism could still occur because of the availability of product, regulatory environment, etc.

**"Available evidence regarding "Big Marijuana" is currently lacking, though regulatory controls can be introduced within regulatory systems to reduce the potential of profit maximization by cannabis retailers."**

The authors clearly aren't well versed in the free market ideology of the United States, where it has proven very difficult to curb industrial interests for the public good. That there are already lobby groups formed to influence government is undisputed. Taking Maryland as an example, we already have the "Maryland Cannabis Industry Association" (Darrell Carrington, CEO), formed for the purposes of representing growers and producers of medical marijuana before the laws have even been implemented in this state. As a perfect case in point, when it became clear that the implementation of the medical marijuana laws were going to be delayed, the Maryland Cannabis Industry Association backed a bill this year for full legalization of the drug (http://baltimore.cbslocal.com/2015/01/30/pot-advocates-promote-legalization-in-maryland/), clearly to protect their current and future monetary investments. Every change they have pushed for with the government appointed panel charged with oversight of the medical program (the Maryland Medical Cannabis Commission) has been in the interests of furthering industrial profits rather than protecting public health (compare current regulations: p. 812 of http://www.dsd.state.md.us/MDR/4213.pdf to original law: http://mgaleg.maryland.gov/webmga/frmMain.aspx?pid=billpage&stab=02&id=hb0881&tab=subject3&ys=2014rs ). Eventually, lawsuits may catch up with the industry from adverse consequences, but meanwhile it will be too late for citizens who may have been harmed, similar to the situation with Big Tobacco and their consumers.