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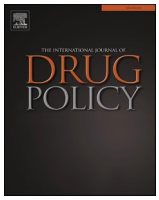

Research Paper

The impact of precursor regulations on illicit drug markets: An analysis of Cunningham et al.'s studies

Luca Giommoni

School of Social Sciences, Cardiff University, Glamorgan Building, King Edward VII Avenue, Cardiff CF10 3WT, United Kingdom

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ABSTRACT

This review examines a series of twelve studies led by James K. Cunningham and his team, focusing on the effects of precursor regulation on illicit drug markets. Their research shows that the regulation of chemicals essential for the production of drugs such as heroin, cocaine, and methamphetamine is associated with several positive outcomes. These include a decrease in drug purity, a reduction in seizures, lower demand for treatment and hospitalization, and an increase in drug prices. According to the research, this decrease in harmful outcomes results from a combination of diminished overall consumption and a reduction in harm per dose. However, this review identifies some inconsistencies within their studies. These inconsistencies include premature assumptions about the timing of intervention impacts, uneven influences of similar interventions, variations in the implementation of these interventions, and the disregard of alternate explanations for sudden shifts in drug markets. Cunningham's work can be considered one of the most substantial contributions in this field. However, to secure the full confidence of the drug policy community in the authenticity of their findings, they must effectively address the issues identified in this review.

Introduction

In a series of twelve studies led by James K. Cunningham, a team of scholars delved into the influence of precursor regulations on illegal drug markets. The findings bring a ray of hope: precursor regulations can significantly curb drug availability and associated harms. These promising outcomes do not only apply to methamphetamines but extended extend to heroin and cocaine. They hold true over several years and across various jurisdictions in North America, with validation through various indicators such as purity, price, hospitalization, and treatment demand.

Despite the premises, the reception of this ground-breaking research has been more of a murmur than a roar in the drug policy community. This relative silence is puzzling, especially considering the dearth of empirical studies that assess the effects of supply-side interventions. Perhaps more importantly, the few analyses that do exist often cast a sceptical eye on these interventions (Pollack & Reuter, 2014), if they do not dismiss them outright as ineffective and harmful (Best et al., 2001; Wood et al., 2003, 2004). Despite its importance, this branch of research is only capturing a sliver of the attention it merits.

This article aims to spotlight Cunningham and his team's work by providing an in-depth analysis of all twelve studies. I start by breaking down what precursor regulations are and how they can disrupt drug markets. This is followed by an analysis of the specific interventions that Cunningham and his team studied, and the methodology that underpins their work. After that, the review illustrates the results of these interventions, and examine the strengths and limitations of these studies. Ultimately, I will articulate strategies to elevate and extend the reach of this line of research.

How chemical and precursor regulations can affect drug markets

The production of illegal drugs necessitates the use of particular chemicals. Two categories of chemicals are involved in the production of these substances: precursors and essential chemicals.

Precursors are the chemical substances that are crucial for the synthesis of an illegal drug, getting integrated into the final molecular structure of the drug. For example, ephedrine is a precursor in the making of methamphetamine. As such, it forms an integral part of the final methamphetamine product (EMCDDA, 2019).

Essential chemicals, instead, encompass all the reagents and catalysts that aid in the creation of a regulated substance. They differ from precursors in that they do not become part of the drug's molecular structure. For instance, the production of cocaine requires oxidising agents like potassium permanganate, and acids such as hydrochloric. These chemicals are essential, yet they do not form part of the end product's molecular structure (Sevick, 1992).

But how does the regulation of essential chemicals and precursors impact drug markets? Regulations targeting precursors are supply-side strategies designed to inflate prices (Reuter & Caulkins, 2003). When

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a new regulation restricting access to precursors and essential chemicals comes into effect, manufacturers are left with a limited set of alternatives. They can either exit the business, find alternative synthesis methods or different chemicals that are not heavily controlled, or resort to other means to procure the same chemical components, such as smuggling or theft. In any case, it is probable that there will be at least a temporary disruption in production until new synthesis methods are firmly established and operate efficiently. This disruption typically results in reduced availability, thereby causing a surge in prices (Babor et al., 2010).

Drug users are price-sensitive, meaning that higher prices lead to decreased consumption (Gallet, 2014; Pacula & Lundberg, 2014; Payne et al., 2020). Importantly, price not only affects the number of users, or the quantity consumed per use, but it is also tied to other drug-related outcomes. Research consistently indicates that when drug prices go up, there is a corresponding decrease in fatal and non-fatal overdoses, emergency department admissions, and hospitalizations (Hughes, Hulme & Ritter, 2020). Evidence about the effects on treatment admissions is, instead, mixed. Theory suggests that as drug prices increase, treatment admissions often decline due to reduced consumption and resultant decreased social issues. However, other factors like service quality and substance type also influence treatment admissions. Fig. 1 provides an illustration of how precursor regulations can affect drug users and drug-related outcomes.

Regulatory actions on essential chemicals and precursors

Cunningham and his team have examined the implications of twenty-six different regulations related to essential chemicals and precursors. Most of these interventions were interrelated, as they either enhanced previously established regulations, addressed shortcomings in existing rules, or aimed to regulate new chemicals that illicit manufacturers began utilizing in response to challenges presented by prior regulations. Of the twenty-six regulations scrutinized, twenty-one focused on methamphetamine production, four on cocaine production, and a mere two targeted heroin production. For a detailed breakdown of these interventions refer to Table 1.

The US Federal government implemented seven out of twenty-two regulations aimed at combating the methamphetamine illicit market in North America. These regulations focused on controlling the diversion of pseudoephedrine and ephedrine, which are key precursors in methamphetamine production. Three of these regulations targeted wholesale distribution by requiring, for example, ephedrine and pseudoephedrine distributors to register with the DEA and maintain records of sales and customers. The remaining four US Federal regulations concentrated on controlling retail sales of ephedrine and pseudoephedrine, found in various sinus and cold medicines. These regulations enforced daily sales limits, recorded purchaser information, and provided guidelines on proper storage.

Cunningham and team also inspected the effects of methamphetamine precursor regulations established in Oregon, Mississippi, and Texas. From 2001 to 2005, Oregon developed three interrelated regulations dictating storage methods for ephedrine and pseudoephedrine, along with additional sales restrictions like mandatory logbook entries for each transaction. Mississippi and Texas instituted comparable limitations in 2005.

The scope of this research extended beyond the US, examining the effects of precursor regulations implemented in Canada and Mexico. In 2003, Canada established two laws mandating licenses for importing, exporting, and distributing ephedrine and pseudoephedrine. A subsequent third regulation imposed limitations on essential chemicals frequently utilized in methamphetamine production.

The analysis also covered four interventions deployed in Mexico. In November 2005, Mexico began reducing pseudoephedrine imports, recognizing that import levels exceeded those needed for legal goods production. This led to further restrictions on pseudoephedrine distribution in 2006 and a total ban in 2008. In addition to these regulatory measures, Cunningham et al. evaluated the impact of shutting down a commercial chemical company accused of illegally importing pseudoephedrine into the country.

More recent studies have further explored the impact of restrictions on essential chemicals required for cocaine and heroin production. The 1989 Chemical Diversion & Trafficking Act regulated potassium permanganate and acetic anhydride, which were commonly used in cocaine and heroin production, respectively. Subsequent regulations were enacted by the US government to address the use of solvents in cocaine production and to regulate sodium permanganate distribution, a potassium permanganate substitute. In 2005, the US Federal government also implemented regulations on the distribution of products containing acetic anhydride mixed with other chemicals that were not covered under the 1989 regulation.

Methodology used in assessing the impact of precursor regulations on illicit drug market

Cunningham and his team evaluate the impact of precursor regulations on illicit drug markets using similar methods. However, they adapt their approach by incorporating different measures, time frames, and geographical units of analysis.

All twelve studies utilize the Autoregressive Integrated Moving Average (ARIMA)-intervention time-series analysis method. This quasi-experimental design evaluates how a series' mean level alters following an intervention, under the assumption that the same ARIMA structure applies before and after the intervention. ARIMA-intervention time-series analysis, compared to simple pre- and post-comparison, accounts for aspects like trend, drift, serial correlation, seasonality, outliers, and the nature of impacts, reducing vulnerability to errors. It is recognized as one of the best methods for establishing causality when random control

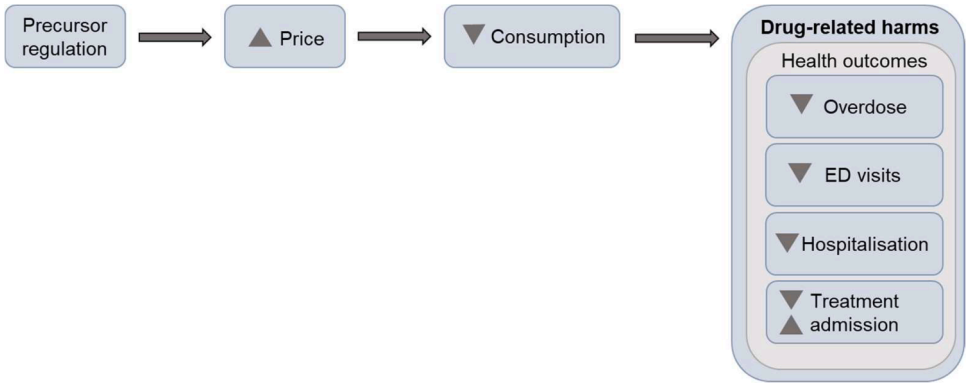

Fig. 1. How precursor regulations impact drug markets.

Table 1
Regulatory actions examined in Cunningham et al.'s studies.

Intervention	Jurisdiction	Implementation	Illicit drug affected	Chemicals	Description
Chemical Diversion & Trafficking Act (CDTA)	Federal US	November 1989	- Cocaine - Heroin - Methamphetamine	Precursors: - Ephedrine - pseudoephedrine Essential chemicals: - acetic anhydride - potassium permanganate - methyl ethyl ketone (MEK) - toluene - ethyl ether - acetone	This legislation obliges providers (such as importers, exporters, manufacturers, and distributors): - To consistently maintain records related to transactions involving essential chemicals, precursor substances, and manufacturing equipment, make these records accessible for inspection, and report any losses or questionable dealings. - Law enforcement agencies are granted the authority to examine records, suspend import or export activities, and disqualify customers. - Notify the appropriate authorities at least 15 days in advance of importing or exporting essential chemicals or precursor substances that surpass a predetermined threshold.
Domestic Chemical Diversion and Control Act (DCDCA)	Federal US	August 1995	- Methamphetamine	In line with the DCDCA	This legislation considerably enhanced reporting and enforcement processes for precursors and essential chemicals, establishing retail-level limitations and security measures for storage (including the placement of retail products behind the counter). The regulations were revised to include products with ephedrine as the sole active ingredient, which were previously exempt from such regulations. Ephedrine (and other precursors) continued to be exempt from regulation when combined with other therapeutic components (i.e., combined products).
Comprehensive Methamphetamine Control Act (MCA) – Phase 1*	Federal US	October 1996	- Methamphetamine	In line with the DCDCA	It governed combined products containing precursors that were previously exempt under the earlier regulations: - Thresholds were established for the wholesale of ephedrine and the retail of combination products containing ephedrine (1 kg and 24 g, respectively), accompanied by enhanced reporting requirements for transactions involving pseudoephedrine, ephedrine, or phenylpropanolamine.
Comprehensive Methamphetamine Control Act (MCA) – Phase 2	Federal US	October 1997	- Methamphetamine	In line with the DCDCA	It governed combined products containing precursors that were previously exempt under the earlier regulations: - Regulations were broadened to encompass products containing pseudoephedrine and phenylpropanolamine, excluding blister packs or other small packaging.
Methamphetamine Anti-Proliferation Act (MAPA)*	Federal US	October 2001	- Methamphetamine	Precursors: - Pseudoephedrine - phenylpropanolamine	The maximum purchase limit for items containing pseudoephedrine or phenylpropanolamine has was decreased from 24 g to 9 g; these products must not be sold in packaging exceeding 3 g of pseudoephedrine or 3 g of phenylpropanolamine.
Combat Methamphetamine Epidemic Act (CMEA) - Phase 1*	Federal US	April 2006	- Methamphetamine	Precursors: - Ephedrine - Pseudoephedrine	The regulation stipulated that: - Ephedrine and pseudoephedrine base sales must not exceed 3.6 g per customer daily; - products should be offered in blister packs containing a maximum of two dosage units each; - monthly sales should not surpass 9 g in total.
Combat Methamphetamine Epidemic Act (CMEA) - Phase 2*	Federal US	October 2006	Methamphetamine	Precursors: - Ephedrine - Pseudoephedrine	The CMEA mandated that - products must be stored either behind the counter or in a locked cabinet; - buyers must present a photo ID; - retailers must document the purchaser's name and address, along with product information, in a logbook
Texas House Bill 164*	Texas, US	August 2005	Methamphetamine	Precursors: - Ephedrine - Pseudoephedrine - Norpseudoephedrine	- Only authorized pharmacies are allowed to conduct over-the-counter sales; sales are restricted to two packages or 6 g; - products must be kept either behind the counter or in a locked case; - buyers must be at least 16 years old, present photo identification, and sign a logbook.
Oregon Store Regulation – Phase 1*	Oregon, US	January 2001	Methamphetamine	Precursors: - Ephedrine - Pseudoephedrine	Oregon prohibited the distribution of over nine grams of ephedrine or pseudoephedrine to any party, excluding specific exempted individuals or organizations (such as physicians, pharmacists, and wholesalers).
Oregon Store Regulation – Phase 2*	Oregon, US	November 2004	Methamphetamine	Precursors: - Pseudoephedrine	Oregon mandated that - standalone pseudoephedrine products be positioned behind a counter and sold exclusively through a pharmacy; - products containing pseudoephedrine combined with another active ingredient be sold only by a pharmacy or non-prescription drug outlet; - buyers present photo identification.
Oregon Store Regulation – Phase 3*	Oregon, US	May 2005	Methamphetamine	Precursors: - Pseudoephedrine	- all pseudoephedrine products be kept in a prescription area or locked storage space within a pharmacy and sold

(*continued on next page*)

Table 1 (*continued*)

Intervention	Jurisdiction	Implementation	Illicit drug affected	Chemicals	Description
					only from a pharmacy; - sellers make a logbook entry for each sale
Oregon Prescription Regulation*	Oregon, US	July 2006	Methamphetamine	Precursors: - Ephedrine - Pseudoephedrine	Designate ephedrine and pseudoephedrine as Schedule III substances, which renders products containing these ingredients accessible solely through a prescription.
Mississippi Store Regulation*	Mississippi, US	July 2005	Methamphetamine	Precursors: - Ephedrine - Pseudoephedrine	- Ephedrine/pseudoephedrine products: - 6 g daily purchase limit for ephedrine/pseudoephedrine - 9 g monthly purchase limit for ephedrine/ pseudoephedrine - Maximum 3 g of ephedrine/pseudoephedrine per package - Single ingredient products: locked display case or behind counter - Combination products: behind counter, within 30 ft of cashiers, locked display case or under video surveillance - Photo identification required for purchase
Mississippi prescription regulation*	Mississippi, US	July 2010	Methamphetamine	Precursors: - Ephedrine - Pseudoephedrine	Designate ephedrine and pseudoephedrine as Schedule III substances, which renders products containing these ingredients accessible solely through a prescription.
Controlled Drugs and Substances – Phase 1	Canada	January 2003	Methamphetamine	Precursors: - Ephedrine - Pseudoephedrine	- Regulation of precursor producers, packagers, and distributors through licensing; - Thorough documentation of the utilization and transfer of precursors
Controlled Drugs and Substances – Phase 2	Canada	July 2003	Methamphetamine	Precursors: - Ephedrine - Pseudoephedrine	- Unlicensed dealers purchasing precursors above a specific limit were required to complete end-use declarations - Verification of the customer's identity was necessary
Controlled Drugs and Substances – Phase 3	Canada	January 2004	Methamphetamine	Essential chemicals: - Acetone - ethyl ether - hydrochloric acid - methylethylketone - sulphuric acid - toluene	- The distribution and sale of crucial chemicals were limited to registered dealers only. - Permits were mandatory for exporting to designated locations, except for preparations containing up to 30 % of precursors. - Documentation requirements were also applied to essential chemicals."
Pseudoephedrine regulation – Phase 1	Mexico	November 2005	Methamphetamine	Precursors: - Pseudoephedrine	- Imports of pseudoephedrine were restricted to align with legitimate consumption
Pseudoephedrine regulation – Phase 2	Mexico	February 2006	Methamphetamine	Precursors: - Pseudoephedrine	- Customers enrolled in a centralized federal database; - daily transaction limit of 60 mg per product; - immediate reporting of theft, loss, diversion, or unusual sales; submission of monthly electronic sales records to the government; - government representatives granted instant access to records upon request.
Rogue company closure	Mexico	March 2007	Methamphetamine	Precursors: - Pseudoephedrine	Authorities pursued legal proceedings against Zhenli Ye Gon, who led the disreputable pharmaceutical corporation, Unimed Pharm Chem de México, on suspicion of unauthorized pseudoephedrine importation. In excess of US$200 million in currency was captured, while the Mexican government filed multiple criminal complaints in connection with falsified import permits for pseudoephedrine.
Precursor Prescription Requirement*	Mexico	September 2007	Methamphetamine	Precursors: - Pseudoephedrine	Prescriptions were required to obtain any pseudoephedrine product in a pharmacy
Precursors ban	Mexico	July 2008	Methamphetamine	Precursors: - Ephedrine - Pseudoephedrine	Mexico has prohibited the use of pseudoephedrine and ephedrine, except for purposes approved by the federal government, such as research, monitoring, and toxicological analysis.
Acetic Anhydride mixture regulation	Federal US	January 2005	Heroin	Essential chemical: - Acetic Anhydride	The 1989 regulation did not cover products with a mix of acetic anhydride and other chemicals. To fix this loophole, a federal rule came into effect on January 14, 2005, regulating any chemical mixture containing more than 20 % acetic anhydride.
Solvent regulation	Federal US	October 1992	Cocaine	Essential chemical: - Sulfuric acid - Hydrochloric acid	Obliges providers (such as importers, exporters, manufacturers, and distributors): - To maintain records related to transactions involving sulfuric acid and hydrochloric acid, make these records accessible for inspection, and report any losses or questionable dealings. - Law enforcement agencies are granted the authority to examine records, suspend import or export activities, and disqualify customers. - Notify the appropriate authorities at least 15 days in advance of importing or sulfuric acid and hydrochloric acid that surpass a predetermined threshold.
MIBK regulation	Federal US	May 1995	Cocaine	Essential chemical: - Methyl isobutyl ketone (MIBK)	This regulation includes methyl isobutyl ketone (MIBK) as a List II Chemical under the Controlled Substances Act. It impacts specific transactions involving over 500 gallons or 1523 kg of MIBK going to countries in the Western

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Table 1 (*continued*)

Intervention	Jurisdiction	Implementation	Illicit drug affected	Chemicals	Description
					Hemisphere, excluding Canada. The affected transactions are: (1) exports; (2) international transactions involving a U.S. broker or trader; and (3) transshipments passing through the U.S.
Sodium Permanganate Regulation	Federal US	December 2006	Cocaine	Essential chemical: - Sodium Permanganate	This regulation specifically focused on sodium permanganate, which is a direct substitute for potassium permanganate. It categorized sodium permanganate as a List II chemical and set thresholds for regulated domestic transactions at $\geq$ 55 kg and international transactions at $\geq$ 500 kg. Chemical distributors had to register with the DEA and maintain records of regulated transactions. If a chemical distributor jeopardized health and safety, the DEA had the authority to revoke its license.

* Regulation controlling retail sales of precursors and essential chemicals.

trials are not feasible or ethical (Schaffer, Dobbins & Pearson, 2021; Lopez Bernal, Cummins & Gasparrini, 2018; Campbell, Cook & Shadish, 2001). Sometimes it even produces results akin to random control trials (Fretheim et al., 2015).

Except for two studies without control series (Cunningham & Liu, 2003; Cunningham, Liu & Callaghan, 2013), all studies contrast the impact of precursor regulation against quasi-control time-series. These control series, unaffected by the intervention in theory, come in two types: series for drugs not affected by the intervention, used in eight out of nine studies, and selected nearby states, used in just one study (Cunningham et al., 2012). Control series help verify that the intervention's impact was specific.

The studies employ a variety of measures to evaluate intervention impacts, including hospital admission, arrest, treatment admission, route of administration, purity, laboratory seizure, drug exhibit chemical composition, past-year and past-month prevalence. Typically, these indicators are analysed independently, with no single study encompassing all. However, two studies concurrently analyse price, purity, and seizures (Cunningham, Liu & Callaghan, 2013; Liu, 2015).

Time series are compiled monthly, with the sole exception for past month and past year prevalence which are quarterly time series. The scope of the analysis is limited to the Unites States in most of the studies (more precisely continental US), with some studies looking specifically at the impact on specific states (California, Arizona, Nevada, Texas, Oregon and Mississippi). Three studies, however, extend the scope of the analysis to Canada and Mexico (Callaghan et al., 2009; Cunningham, Liu & Callaghan, 2009). In few instances, the authors draw conclusions from the comparison of specific US geographic area (e.g., Southern v Midwest) or with the Hawaii. The availability of data also drives the length of the time series, with some studies analysing time-series from 1983 to 2000 and others from 2000 to 2011.

Evaluating regulatory effects on methamphetamine, cocaine, and heroin markets

This section offers a brief overview of the outcomes from various studies by Cunningham and colleagues on precursor regulations, all of which are summarized in Table 2.

The trio of U.S. federal regulations aimed at limiting wholesale methamphetamine production had significant ripple effects on both supply and demand. The 1989 Chemical Diversion and Trafficking Act corresponded with a 35 % decrease in meth-related hospital admissions and arrests in California, as well as a 17-percentage point dip in the purity of meth nationwide (Cunningham & Liu, 2003, 2005; Cunningham, Liu & Callaghan, 2009).

The 1995 Domestic Chemical Diversion Control Act was even more disruptive. The law coincided with an 18 % drop in meth purity, 48 % fewer hospital admissions, and a 51 % reduction in arrests. Similar changes were also observed in Arizona and Nevada (Cunningham & Liu, 2003, 2005, 2008).

Findings from the 1997 Comprehensive Methamphetamine Control Act align with the patterns observed in the previous interventions, with a decline in meth's purity leading to fewer meth-related harms and arrests. Interestingly though, this regulation did not impact the demand for treatment in Texas. This could be attributed to two key factors: the extremely small number of Texans seeking treatment for meth abuse, and the continued meth supply from Mexico (Cunningham et al., 2010).

Notably, these regulations influenced how methamphetamine was consumed, with methods traditionally linked to the US declining in favour of smoking, which is more common in Mexico (Cunningham, Liu & Muramoto, 2008). A quicker recovery in the Southwest was also observed, which is likely due to easier access to precursors from Mexico. These regulations, instead, did not affect the methamphetamine market in the Hawaii where clients prefer high-purity "Ice"(Cunningham, Liu & Callaghan, 2009).

The four federal regulations targeting retail sales of ephedrine and pseudoephedrine had little to no impact on methamphetamine use indicators.

State-level regulations were gauged through metrics like Texas' voluntary treatment admissions and lab seizures in Oregon and Mississippi. The 2005 Texas House Bill 164 did not have any effect. In Oregon, only one 2005 store regulation reduced lab seizures by 47 %. Both store and prescription regulations in Mississippi significantly reduced lab seizures by 63 % and 50 %. The variances were attributed to the different maturity levels of each state's market (Cunningham et al., 2012).

The results regarding the three Canadian regulations are unexpected and somewhat puzzling. Both January and July 2003 regulations led to an increase in methamphetamine purity by 16 and 14 percentage points respectively within the continental U.S. However, the 2004 regulation saw a decrease in purity by 14 percentage points. In Canada, while the January 2003 regulation had no significant impact on acute-care hospital admissions, the July 2003 and 2004 regulations coincided with a surge of 20 % and 21 % respectively (Callaghan et al., 2009; Cunningham, Liu & Callaghan, 2009).

Callaghan's team suggests a 'substitution theory' to explain these results. They propose that sophisticated organizations likely overtook small-scale ones. In the U.S., meth production possibly shifted from local labs to large Mexican producers. This criminal upgrade could explain these anomalies. The 2004 regulation possibly affected both Mexican and American producers, reducing meth purity in the US. The divergent trends between the U.S. and Canada can be attributed to the fact that Canada does not import methamphetamine from the U.S. or Mexico, but rather operates as an autonomous entity.

The outcomes of Mexican regulations are multifaceted, with only two interventions achieving their goals. The 2005 pseudoephedrine regulation coincided with an 11 % decrease in treatment admissions in Texas and a 12 % decrease in Mexico (Cunningham et al., 2010). Exhibits for the powerful D-methamphetamine fell by 40 %, while less potent types surged (Cunningham et al., 2013).

Table 2
Summary of the evidence from Cunningham et al.'s research.

Intervention	Substance	Outcome measure	Jurisdiction	Effect[a]	Control	Study
1989 US CDTA	Methamphetamine	Hospital admission	California	−35 %	NA	(Cunningham & Liu, 2003)
		Arrests	California	−44 %	Decline in heroin and cocaine, but not for marijuana	(Cunningham & Liu, 2005)
		Purity	Continental US	−16.57pp	Decline in heroin and cocaine purity.	(Cunningham, Liu & Callaghan, 2009)
	Heroin	Purity	Continental US	−40 %	NA	(Cunningham, Liu & Callaghan, 2013)
		Price	Continental US	93 %	NA	
		Seizures	Continental US	−27 %	NA	
	Cocaine	Purity	Continental US	−4 %	Decline for methamphetamine and heroin, but not for marijuana	(Cunningham, Callaghan & Liu, 2015)
		Price	Continental US	36 %	Increase for methamphetamine and heroin, but not for marijuana	
		Seizures	Continental US	−28 %	Decline for methamphetamine and heroin, but not for marijuana	
1995 US DCDCA	Methamphetamine	Hospital admission	California	−48 %	NA	(Cunningham & Liu, 2003)
			Arizona	−71 %	NA	
			Nevada	−52 %	NA	
		Arrests	California	−51 %	No change for marijuana, heroin or cocaine	(Cunningham & Liu, 2005)
		Voloutary Treatment admission	California	−39 %	No change for alcohol, heroin or cocaine	(Cunningham & Liu, 2008)
		Route of administration: snorting	California	−50 %	No change in route of heroin administration	(Cunningham, Liu & Muramoto, 2008)
		Route of administration: Smoking	California	−43 %	No change in route of heroin administration	
		Route of administration: Swallowing	California	−26 %	No change in route of heroin administration	
		Route of administration: Injecting	California	−26 %	No change in route of heroin administration	
		Purity	Continental US	−67.91pp	No change for heroin. Slight decrease for cocaine	(Cunningham, Liu & Callaghan, 2009)
1996 US MCA	Methamphetamine	Hospital admissions	California	–	NA	(Cunningham & Liu, 2003)
			Arizona	–	NA	
			Nevada	–	NA	
		Arrests	California	–	No change in marijuana, heroin or cocaine	(Cunningham & Liu, 2005)
		Route of administration: Smoking	California	40 %	No change in route of heroin administration	(Cunningham, Liu & Muramoto, 2008)
		Purity	Continental US	–	No change in heroin or cocaine purity	(Cunningham, Liu & Callaghan, 2009)
1997 US MCA	Methamphetamine	Hospital admission	California	−53 %	NA	(Cunningham & Liu, 2003)
			Arizona	−25 %	NA	
			Nevada	−77 %	NA	
		Arrests	California	−60 %	No change in cocaine, heroin or marijuana	(Cunningham & Liu, 2005)
		Voloutary Treatment admission	California	−31 %	No change in cocaine, heroin or alcohol	(Cunningham & Liu, 2008)
		Route of administration: snorting	California	−38 %	Brief decline in number of heroin smokers	(Cunningham, Liu & Muramoto, 2008)
		Purity	Continental US	−28.94pp	No change for heroin or cocaine	(Cunningham, Liu & Callaghan, 2009)
		Voloutary Treatment admission	Texas, US	–	No change for cocaine, heroin, and alcohol admissions	(Cunningham et al. 2010)
2001 US MAPA	Methamphetamine	Purity	Continental US	–	Increase in cocaine but not heroin	(Cunningham, Liu & Callaghan, 2009)
		Voloutary Treatment admission	Texas, US	–	Increase for heroin, cocaine and alcohol	(Cunningham et al., 2010)
01/03 Canada Controlled Drugs and Substances	Methamphetamine	Purity	Continental US	+15.70pp	No change for heroin or cocaine	(Cunningham, Liu & Callaghan, 2009)
		Acute-care hospital admission	Canada	–	No change for cocaine, heroin/opioids, alcohol	(Callaghan et al., 2009)
07/03 Canada Controlled Drugs and Substances	Methamphetamine	Purity	Continental US	+13.68pp	No change for heroin or cocaine	(Cunningham, Liu & Callaghan, 2009)
		Acute-care hospital admission	Canada	20 %	No change for cocaine, heroin/opioids, alcohol	(Callaghan et al., 2009)
2004 Canada Controlled Drugs and Substances	Methamphetamine	Purity	Continental US	−13.87pp	No change for heroin or cocaine	(Cunningham, Liu & Callaghan, 2009)
		Acute-care hospital admission	Canada	21 %	No change for cocaine, heroin/opioids, alcohol	(Callaghan et al., 2009)

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Table 2 (*continued*)

Intervention	Substance	Outcome measure	Jurisdiction	Effect[a]	Control	Study
11/05 Mexico Pseudoephedrine regulation	Methamphetamine	Voloutary Treatment admission	Texas, US	−11 %	Little/no change for cocaine, heroin and alcohol admission	(Cunningham et al., 2010)
		Treatment admission	Mexico	−12 %	No change for cocaine, heroin and alcohol admission	
		% d-methamphetamine exhibits	Continental US	−40.50 %	Little/no change for heroin, cocaine and marijuana	(Cunningham et al., 2013)
		Past year prevalence [b]	Continental US	–	No change heroin and marijuana	(Cunningham, Liu, & Callaghan 2016)
		Past month prevalence [b]	Continental US	–	No change heroin and marijuana	
03/07 Mexico Rogue company closure	Methamphetamine	Voloutary Treatment admission	Texas, US	−48 %	Little/no change for cocaine, heroin and alcohol admission	(Cunningham et al., 2010)
		Treatment admission	Mexico	−56 %	No change for cocaine, heroin and alcohol admission	
		% d-methamphetamine exhibits	Continental US	−26.60 %	Little/no change for heroin, cocaine and marijuana	(Cunningham et al., 2013)
		Past year prevalence [b]	Continental US	−35 %	No change heroin and marijuana	(Cunningham, Liu, & Callaghan, 2016)
		Past month prevalence [b]	Continental US	−45 %	No change heroin and marijuana	
09/07 Mexico Precursor Prescription Requirement	Methamphetamine	Voloutary Treatment admission	Texas, USA	–	Little/no change for cocaine, heroin and alcohol admission	(Cunningham et al., 2010)
		Treatment admission	Mexico	–	No change for cocaine, heroin and alcohol admission	
		% d-methamphetamine exhibits	Continental US	–	Little/no change for heroin, cocaine and marijuana	(Cunningham et al., 2013)
2008 Mexico Precursor Ban	Methamphetamine	Voloutary Treatment admission	Texas, USA	–	Little/no change for cocaine, heroin and alcohol admission	(Cunningham et al., 2010)
		Treatment admission	Mexico	−15 %	No change for cocaine, heroin and alcohol admission	
		% d-methamphetamine exhibits	Continental US	–	Little/no change for heroin, cocaine and marijuana	(Cunningham et al., 2013)
2005 Texas House Bill 164	Methamphetamine	Voloutary Treatment admission	Texas, USA	–	Little/no change for cocaine, heroin and alcohol admission	(Cunningham et al., 2010)
01/2005 Mexico determines increase precursor control	Methamphetamine	% d-methamphetamine exhibits	Continental US	−62 %	Little/no change for heroin, cocaine and marijuana	(Cunningham et al., 2013)
02/2006 Domestic Distribution Restriction	Methamphetamine	% d-methamphetamine exhibits	Continental US	–	Little/no change for heroin, cocaine and marijuana	
2002 Oregon store regulation	Methamphetamine	Laboratory seizures	Oregon, US	–	No change for Washington, California and	(Cunningham et al., 2012)
2004 Oregon store regulation			Oregon, US	–	Nevada. Idaho introduce precursor reg at the same time of Oregon	
2005 Oregon Store Regulation			Oregon, US	−47 %		
2006 Oregon Prescription Regulation			Oregon, US	–		
2005 Mississippi store regulation			Mississippi, US	−63.40 %	No change for nearby states. Florida introduce precursor reg at the same time of Mississippi	
2010 Mississippi prescription regulation			Mississippi, US	−50.20 %		
04/06 US CMEA	Methamphetamine	Laboratory seizures	Oregon, US	–	No change for nearby states. Idaho introduce precursor reg at the same time of Oregon	
			Mississippi, US	–	No change for nearby states. Florida introduce precursor reg at the same time of Mississippi	
10/06 US CMEA	Methamphetamine	Laboratory seizures	Oregon, US	–	No change for nearby states. Idaho introduce precursor reg at the same time of Oregon	
			Mississippi, US	–	No change for nearby states. Florida introduce precursor reg at the same time of Mississippi	
2005 US Acetic anhydride mixture regulation	Heroin	Purity	Continental US	–	NA	(Cunningham, Liu & Callaghan, 2013)
		Price	Continental US	–	NA	
		Seizures	Continental US	–	NA	
1992 US Solvent regulation	Cocaine	Purity	Continental US	–	No alterations for marijuana, heroin; methamphetamine changes due to targeted interventions	(Cunningham, Callaghan & Liu, 2015)
		Price	Continental US	–		
		Seizures	Continental US	−29 %		

(*continued on next page*)

Table 2 (*continued*)

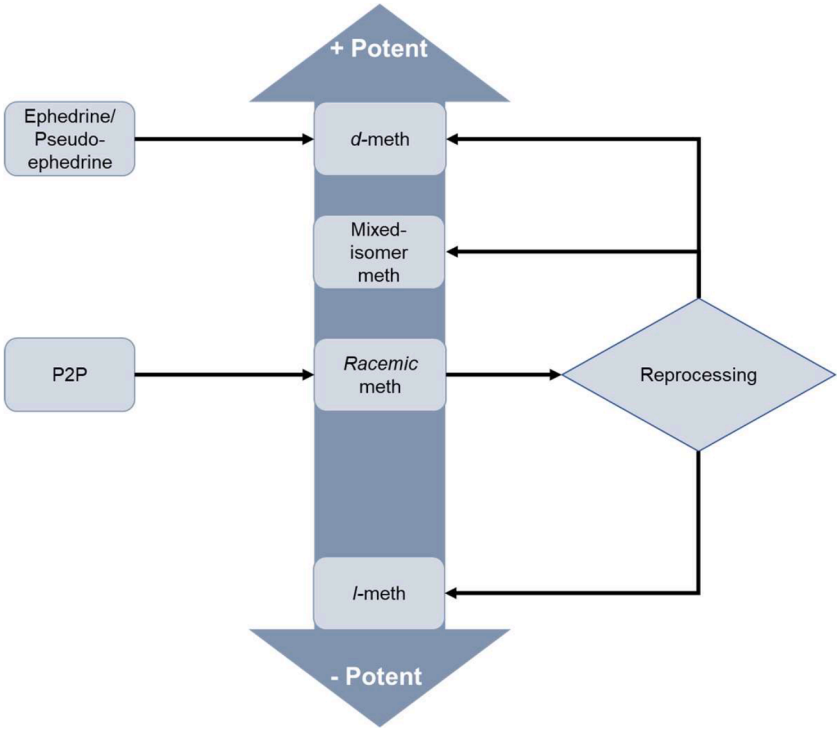
Intervention	Substance	Outcome measure	Jurisdiction	Effect[a]	Control	Study
1995 US MIBK regulation	Cocaine	Purity	Continental US	–	No alterations for marijuana, heroin; methamphetamine changes due to targeted interventions	(Cunningham, Callaghan & Liu, 2015)
		Price	Continental US	25 %		
		Seizures	Continental US	–		
2006 US Sodium Permanganate Regulation	Cocaine	Purity	Continental US	−35 %	No alterations for marijuana, heroin; methamphetamine changes due to targeted interventions	(Cunningham, Callaghan & Liu, 2015)
		Price	Continental US	100 %		
		Seizures	Continental US	−22 %		
		Past year prevalence [b]	US	−32 %	No change heroin and marijuana	(Cunningham, Liu, & Callaghan, 2016)
		Past month prevalence [b]	US	−29 %	No change heroin and marijuana	

[a] Estimates based on ARIMA model predictions;.
[b] Quarterly Time Series.

Remarkably, shutting down a company in Mexico, which was covertly trafficking precursors, had a drastic effect on the meth market. Treatment admissions plummeted by 48 % and 56 % in Texas and Mexico respectively. Additionally, *d*-methamphetamine exhibits fell by 20 %, and there was a 35 % drop in yearly prevalence and a 45 % drop in monthly prevalence - effects not seen with the 2005 pseudoephedrine regulation (Cunningham, Liu, & Callaghan, 2016).

Conversely, the 2008 ban on ephedrine and pseudoephedrine had the least impact, causing negligible alterations in U.S. indicators and

Box 1. Methamphetamine production and isomer composition



Methamphetamine molecules occur in two isomeric forms: *d*-methamphetamine and *l*-methamphetamine. When synthesized using either ephedrine or pseudoephedrine, the result is primarily *d*-methamphetamine. In contrast, synthesis via phenyl-2-propanone, yields a 50:50 blend of both isomers, *d*-methamphetamine and *l*-methamphetamine, commonly referred to as racemic methamphetamine. However, *l*-methamphetamine is generally less sought-after.

Racemic methamphetamines necessitate an extra purification step at the end of the synthesis process to isolate the more potent *d*-methamphetamine, or alternatively, to produce a substance where the concentration of *d*-methamphetamine exceeds 50% - referred to as mixed isomer methamphetamine.

Cunningham and colleagues (2013) show that when ephedrine or pseudoephedrine were regulated in Mexico, there was a noted decrease in *d*-methamphetamine exhibits. Conversely, there was an increase in racemic, *l*-methamphetamine, and mixed-isomer methamphetamine.

only a 15 % decrease in Mexican treatment admissions. As seen in many other instances, regulations on prescription requirements did not produce significant shifts in methamphetamine indicators.

The 1989 CDTA and 2006 Sodium Permanganate Regulation, both targeting cocaine production, saw the most significant changes in cocaine-related metrics (Cunningham, Callaghan & Liu, 2015; Cunningham, Liu, & Callaghan, 2016). The former was linked with a 4 % purity decrease, 28 % fewer seizures, and a price surge of 36 %. The latter achieved a steeper 35 % drop in purity, a 22 % decrease in seizures, a 32 % reduction in past year prevalence, and a 29 % decline in past month prevalence, even as cocaine prices doubled. The results of the other two regulations are less straightforward. The 1992 solvent regulation led to a 29 % reduction in seizures without affecting price or purity. The 1995 MIBK regulation resulted in a 25 % price increase, but no noticeable shifts in purity or seizures.

The 1989 CDTA had significant impacts on heroin production, including a 40 % drop in purity, a 27 % decrease in seizures, and a shocking 93 % price hike (Cunningham, Liu & Callaghan, 2013). This regulation notably targeted Acetic Anhydride, a crucial ingredient in heroin manufacturing. However, the 2005 U.S. regulation on Acetic Anhydride mixtures did not bring any observable shift in heroin availability.

As we conclude this section, it is important to emphasize that the disruptions caused by these interventions have had enduring effects spanning several years. Empirical research indicates that supply-side interventions are generally fleeting, with markets often rebounding promptly once these interventions cease (Mazerolle, Soole & Rombouts, 2006). Cunningham and his team have demonstrated that the durations of some of these interventions, such as the 1989 CDTA, ranged between one to three years for substances like methamphetamine, heroin, and cocaine. Even more startlingly, both the Mexican precursor regulations and the US 2006 Sodium Permanganate Regulation had effects persisting up to eight years. The impacts of these interventions were not only immediate and profound, but also had enduring consequences.

In praise of Cunningham et al.'s research

Cunningham and his team have demonstrated something that has long been a point of contention in the drug policy community: supply-side interventions can indeed reduce drug availability and related harms. Based on the evidence provided, these interventions have saved numerous methamphetamine, cocaine, and heroin users from hospitalization or even death. The even better news? We can accomplish this without resorting to imprisonment, which not only drains taxpayer money but also restricts opportunities for those arrested. Rather, we can achieve these outcomes through administrative and bureaucratic measures that regulate the trade of specific chemicals.

In addition to illustrating the disruptive power of precursor regulation, these studies reveal two more crucial insights. Firstly, not all precursor regulations are successful. Knowing what does not work is just as valuable as knowing what does. For instance, the 1997 CMCA resulted in a 31 % drop in treatment admissions in California, but had no effect in Texas due to the low demand for treatment there (Cunningham & Liu, 2008; Cunningham et al., 2010). As highlighted in previous commentaries, context matters - the same intervention can yield different outcomes based on local circumstances (McKetin, 2009). Similarly, the preference for 'Ice' in Hawaii obscured the potential impact of these regulations. However, a deeper investigation into price shifts could have provided insight into the true impact of these regulatory measures. Ultimately, interventions with an ill-focused scope, particularly those targeting minor-scale manufacturers, show little promise in affecting the availability of methamphetamine or reducing harm to users.

Secondly, Cunningham and his team have shed light on a previously overlooked aspect of how supply-side interventions can reduce users' harm. Regulating precursors can lead to the production of less harmful types of methamphetamine and safer methods of consumption (refer to Box 1 for a more comprehensive understanding of methamphetamine production and its isomer composition). This reduction in harmful outcomes is due to both an overall decrease in consumption and a decrease in harm per dose. While it is challenging to determine which factor plays a larger role, a 40 % decrease in the most harmful meth isomeric composition could partially explain the significant reduction in treatment admissions - even in the absence of any change in prevalence for the 2005 pseudoephedrine regulation in Mexico (Cunningham et al., 2013; Cunningham, Liu, & Callaghan, 2016). When access to key precursors is restricted, users are forced to resort to alternative chemicals, which result in less potent drugs.

Moreover, these policies inadvertently contribute to the adoption of safer consumption methods. Restricting access to domestic precursors led to a decrease in domestic production and an increase in methamphetamine supply from Mexico. The mode of consumption evolved alongside the new supply, with smoking - typical in Mexico - becoming more prevalent in the U.S. as the distribution of Mexican-produced methamphetamine increased. In contrast, injecting, considered the riskiest consumption method and more typical of domestic methamphetamine production, fell out of favor (Cunningham, Liu & Muramoto, 2008).

These shifts in consumption modes and potency following precursor regulations underscore the gaps in our understanding of supply-side interventions. Gaps that Cunningham and his team have effectively helped bridge.

Inconsistencies in Cunningham et al's research

This section critically examines Cunningham et all's research, not to discredit their findings, but because of their importance. Misinterpreted studies can cause more harm than a lack of empirical analysis. While these criticisms apply to several of their studies, they do negate their overall value.

Cunningham's team leap to the conclusion that intervention impacts occur simultaneously with their implementation. At the very least, this assumption is dubious, particularly in the case of cocaine and heroin. Based on available evidence, the journey from cultivating coca in Colombia to its arrival on American streets takes between 18 and 24 months (Ehleringer et al., 2011, 2012). A similar time-lag may be expected for heroin. This begs the question of how these regulations can instantly impact the retail price and purity of cocaine and heroin. Can an intervention, affecting the initial stages of the supply chain, ripple through to the retail market 4000 km away, without any delay? The authors attribute this immediate impact to a lack of chemical stockpiles. Their argument is thus: the moment a drug manufacturer in Colombia faces difficulties processing cocaine, a dealer in New York adjusts prices and purity levels. This explanation might hold some merit in the case of methamphetamine, where the production-to-consumption chain is notably shorter. However, for cocaine and heroin, it is far less plausible. If we consider even a shorter delay, say 6–12 months, it could call for a re-evaluation of Cunningham and team's conclusions. If they aim to convince the drug policy community about the effects of precursor policies on cocaine and heroin, addressing this potential issue is crucial.

Second, Cunningham and his team quickly dismiss alternative explanations for the sudden shift in the cocaine market that started in 2007, attributing it to the US Sodium permanganate regulation. However, other contributing factors may have been at play. Specifically, Juan Manuel Santos's appointment as Colombia's defence minister in July 2006 ushered in a radical change in the country's anti-drug strategies. Santos and his team pivoted from emphasizing aerial spraying and manual eradication to prioritizing the disruption of cocaine production and trafficking. As a result of this shift, cocaine seizures increased by 60 % and laboratory shutdowns rose by 26 % between 2006 and 2009. This new approach was found to be a more effective and economically efficient anti-narcotics policy, as assessed by Mejía (2016). Cunningham and his team also overlooked findings from other studies

that offer alternative explanations for the abrupt decline in cocaine use in the US (Caulkins et al., 2014). These factors were not adequately acknowledged in their research.

Third, there is a confusing inconsistency in Cunningham and his team's operationalization of Mexican interventions across their studies. In two of them (Cunningham et al., 2010; Cunningham, Liu, & Callaghan, 2016), they set November 2005 as the starting point for the pseudoephedrine restrictions, coinciding with when Mexico started curtailing pseudoephedrine imports to match legitimate consumption. Yet, in their 2013 study, they suddenly backtrack to January 2005, noting it as the period when Mexico resolved to bolster precursor control. What is intriguing is why this date was only featured in one out of three studies, and why an intention to regulate precursors was considered an intervention. The choice to regard January 2005 as the inception of interventions in the 2013 study curiously aligns with a swift shift in methamphetamine exhibit trends, a pattern not detected in the other studies. Although there is no proof suggesting deliberate data manipulation to bolster their narrative, the authors might want to shed some light on this discrepancy in their research design.

Lastly, the team's work presents some inconsistencies regarding how the same or similar interventions influence drug markets, alongside contrasting findings about the same interventions' impacts. To illustrate, Canada rolled out three distinct regulations between January 2003 and January 2004. Interestingly, the first two seemed to boost methamphetamine purity in the US, while the last caused a decrease (Cunningham, Liu & Callaghan, 2009). It is challenging to reconcile why three closely-timed interventions would lead to such divergent results. This is especially confounding given that the first two directly targeted ephedrine and pseudoephedrine, while the last pertained to chemical precursors, which are generally viewed as less critical in methamphetamine production.

Further fuelling the surprise is the outcome from the analysis of acute hospital admissions in Canada (Callaghan et al., 2009). These admissions rose by 20 % following the July 2003 and January 2004 interventions, a result that runs counter to previous studies. One possible explanation proposed is the emergence of larger, more sophisticated groups capable of producing higher-quality methamphetamine. Yet, this idea stands in contrast with other research indicating a growing number of sellers, importers, and exporters in Canada from 1999 to 2009 (Bouchard et al., 2019). The overarching narrative regarding Canadian regulation comes across as inconsistent, seemingly lacking the empirical backing needed to substantiate how it operates.

This analysis does not encompass every potential concern with Cunningham et all's research. I have highlighted the most critical issues I believe could undermine their scholarship if not thoroughly addressed. Earlier commentaries have pointed out other problems, including a lack of clarity about the durations of these impacts, the extent to which these regulations were actually implemented and enforced, and the temporal clustering of these interventions, which complicates efforts to isolate individual effect (Reuter & Caulkins, 2003; Caulkins, 2009, 2015, 2016; McKetin, 2009; Mcketin, 2008; McKetin et al., 2011).

Conclusions

Cunningham et all's work has been heralded by Caulkins as the 'most significant drug policy paper of this century'(2015, 110). Caulkins urges everyone concerned with drug policy to read and debate this research. However, it seems that this influential paper has yet to make a significant impact, with only 23 citations at the time of this writing. This lack of attention is concerning, considering the research's potential to save numerous lives with minimal investment. My hope is that this commentary will cast a spotlight on Cunningham et all's work, attracting the attention it merits.

Caulkins also pointed out that if this study does not claim the title of the century's most crucial drug policy research, then it must be wrong. To be clear, I have no evidence to declare their research wrong. Some of their conclusions, particularly those examining the impact of US regulations against methamphetamine in the 90 s, are convincingly substantiated and corroborated by other studies (Dobkin & Nicosia, 2009).

Nonetheless, certain issues permeate the analysis of the Canadian and Mexican regulations, as well as those regarding cocaine and heroin. These issues do not necessarily invalidate their research, but they must be addressed if Cunningham and his team aim to persuade the drug policy community of their findings.

Until the evidence suggests otherwise, we owe a debt of gratitude to Cunningham et al. Their work has greatly enhanced our understanding of supply-side interventions and precursor control.

Caulkins, in 2015, suggested three avenues for refining Cunningham et all's research: reproduction of their studies, confirmation through analysis of other countries' time-series data, and introduction of alternative forms of evidence, such as qualitative data. I propose three additional strategies.

Firstly, future studies should be pre-registered. Given the significance of this work, every measure should be taken to avoid data overfitting and overly specific sample-dependent conclusions. Preregistration enhances transparency and rigor, which in turn bolsters confidence in the results.

Secondly, it is time for a fresh systematic review on precursor control. With over a decade passing since McKetin et al.'s review (2011), the research landscape has evolved significantly. We need to catch up and fold in these new insights.

Third, we need to explore whether these regulations can provoke any side effects to the legal economy and wider society. Almost all the chemicals covered here have numerous uses in the legitimate economy. For instance, ephedrine is used for producing cold tablets and diet pills while MEK is used in the production of plastic and pharmaceuticals. Does restricting access to these chemicals make producing certain legal goods harder and more expensive? Policy makers may accept this as a side-effect of these regulations, but they need to know it.

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Luca Giommoni: Conceptualization, Data curation, Funding acquisition, Resources, Writing – original draft, Writing – review & editing.

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