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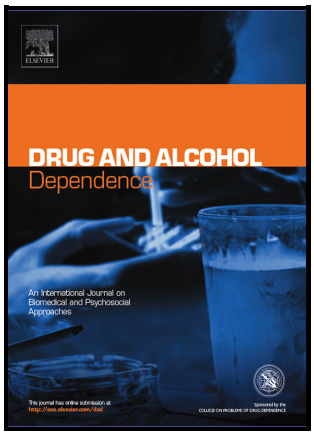

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Does Regulating Drug Precursors Affect Illicit Drug Markets? An Expanded and Updated Systematic Review

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Abstract

Background: Many countries are placing greater emphasis on regulating precursor chemicals used in illicit drug production. However, the latest review on this topic is 14 years old and limited to North American methamphetamine regulations. This review updates and expands on past work by assessing how precursor regulations affect illicit drug markets.

Method: We conducted a systematic review following PRISMA guidelines, searching 13 databases and relevant organizational websites for grey literature. Eligible studies quantitatively assessed precursor regulations' impact on drug supply, demand, or related harms. Due to intervention variability, we used narrative synthesis. Bias risk was evaluated with the EPOC Risk of Bias Tool.

Results: Twenty-six studies met the inclusion criteria, published between 2003 and 2023, focusing on methamphetamine (n=23), cocaine (n=3), and heroin (n=1). Most were from the USA (n=20), with others from Canada (n=1), Mexico (n=1), Australia (n=3), and the Czech Republic (n=1). The studies assessed 12 outcomes across 37 interventions, 14 of which were effective and 23 ineffective. Effective interventions led to impacts such as a 100% price increase, a 40% purity reduction, and a 43% drop in past-month drug use, lasting from months to seven years. Ineffective interventions shared three issues: targeting unused

chemicals, focusing on small-scale operations, or failing as suppliers adapted to new sources or routes.

Conclusions: Precursor regulations can reduce the supply, use, and harms of heroin, cocaine, and methamphetamine. However, they are not a one-size-fits-all solution. Their effectiveness depends on how they are designed and the context in which they are implemented.

Key words
Precursors; Regulations; Supply-side interventions

Introduction

Controlling precursor chemicals is becoming key in tackling illegal drug markets, especially with the increase in synthetic drugs. “First, we can accelerate efforts to regulate the precursor chemicals that are used to illicitly make synthetic drugs” said former Secretary Antony J. Blinken at the UN Commission on Narcotic Drugs on March 15, 2024 (U.S. Department of States, 2024). This was considered the first step in addressing the synthetic opioid crisis, which caused 74,702 overdose deaths in the United States in 2023 (Centers for Disease Control and Prevention, 2024). Controlling these chemicals is also a key part of the European Union Roadmap to fight Drug Trafficking and Organised Crime (European Commission, 2023).

There are two types of chemicals used in making illicit drugs: precursors and essential chemicals (EMCDDA, 2019). Precursors are chemicals that become part of the final structure of the drug. For example, ephedrine is commonly used to produce methamphetamines. Essential chemicals, on the other hand, are reagents and catalysts needed for production but do not become part of the drug’s structure. For instance, making cocaine requires oxidizing agents like potassium permanganate.

The goal of precursor control is to prevent these chemicals from being diverted from legal uses to making illegal drugs. Limiting access to key chemicals is meant to

disrupt the supply chain, reducing availability and increasing the retail price of illegal drugs (Bouchard and Ponce, 2024; Reuter and McKetin, 2024). Higher prices lead to lower consumption (Gallet, 2014; Payne *et al.*, 2020), so precursor control can also reduce drug-related harms, such as overdoses (Babor *et al.*, 2010; Hughes, Hulme and Ritter, 2020).

There is a lack of systematic and up-to-date knowledge on how precursor regulation impacts illicit drug markets. The last systematic review (McKetin et al., 2011) was conducted 14 years ago and focused only on the regulation of chemicals for methamphetamine production. Its evidence was limited to North America, specifically the United States, Canada, and Mexico. Since then, new studies have looked at the impact of regulating chemicals for heroin and cocaine production (Cunningham, Liu and Callaghan, 2013, 2016; Delcher et al., 2017). Research has also examined the effects of regulating precursors in Europe and Australia (Ferris et al., 2016; Mazerolle et al., 2017; Petruželka and Barták, 2020). Clearly, the United States is not the only country grappling with drug-related challenges, nor is methamphetamine the only substance driving fatal overdoses (Jalal et al., 2018). Are precursor controls effective tools for addressing markets beyond methamphetamine and beyond U.S. borders? To answer this, recent reviews (Bouchard and Ponce, 2024; Giommoni et al., 2024; Nicosia and Smart, 2024) urge expanding McKetin et al.'s work by adding new findings and a wider range of contexts.

This systematic review aims to evaluate how effective regulations on drug precursors are at influencing the supply, use, and related harms of illicit drugs. It synthesises key evidence from past regulatory efforts and highlights challenges for future policies.

Method

We conducted this systematic review following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (Page *et al.*, 2021). The protocol was registered on PROSPERO (Giommoni *et al.*, 2024). Research ethics approval was not required.

Search Strategy

We conducted a systematic search of thirteen electronic databases in consultation with

an academic librarian. The databases included: Web of Science, Scopus, APA PsycInfo, EconLit, Google Scholar (first 1000 hits), Social Science Premium Collection, Criminal Justice Abstracts, Social Science Research Network, JSTOR, PubMed, Science Direct, OpenGrey, ProQuest Dissertations and Theses Global. To ensure comprehensive coverage we also hand-searched websites of relevant organizations (ISSDP, UNODC, EMCDDA, RAND Corporation, and National Drug Law Enforcement Research Fund).

We identified potentially eligible studies additionally by consulting experts in the field of drug policy. The initial list of experts was expanded to include the authors of studies deemed eligible after full-text screening. Furthermore, we reviewed the bibliographies of potentially eligible studies and incorporated relevant references into the full-text screening process.

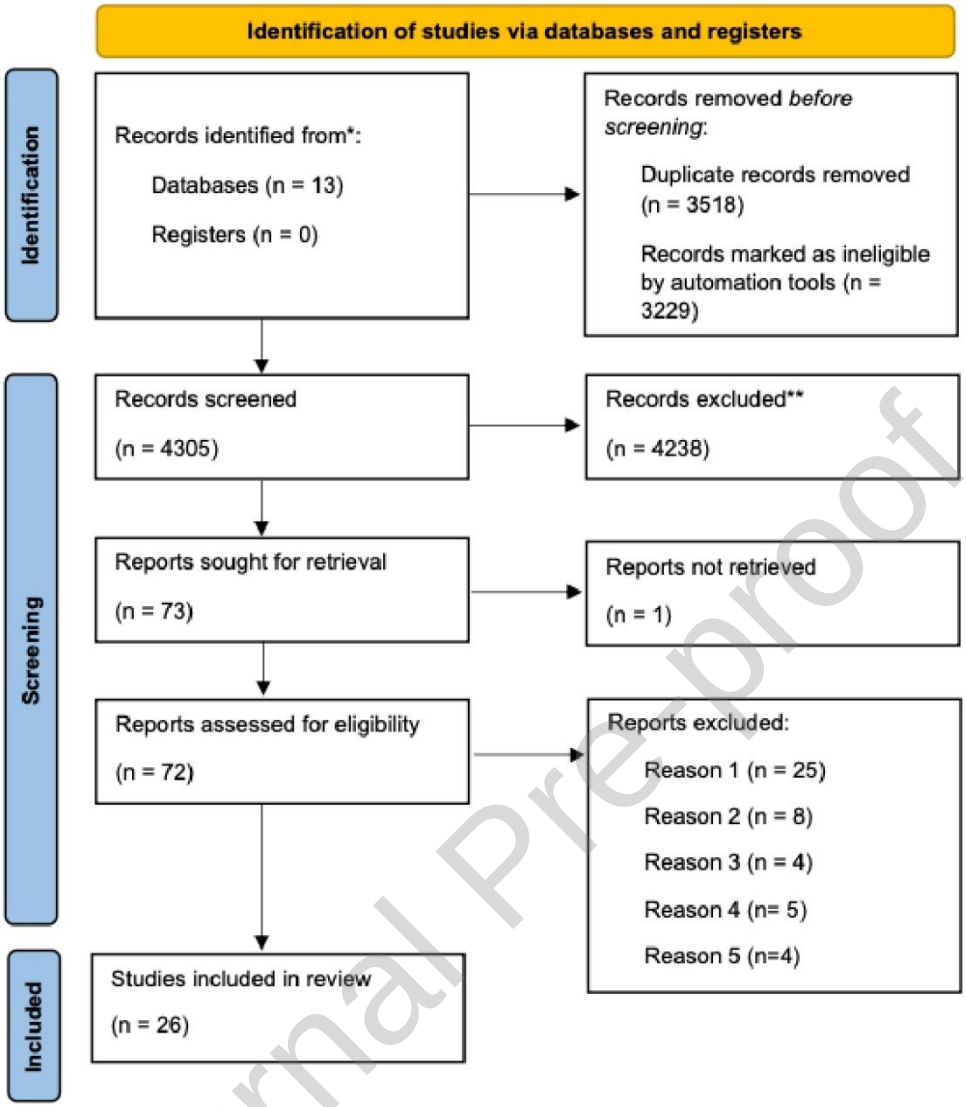
The search strategy combined terms related to precursor regulations and illicit drugs, using both controlled vocabulary and free-text terms (Annex 1). The final search was conducted on February 29, 2024, with no publication date restrictions.

Inclusion Criteria

We included only quantitative studies that examined regulations on chemicals used in the production of illicit drugs, such as precursors and essential chemicals. Eligible studies focused on the impacts of these regulations on drug supply (e.g., arrests and seizures), drug demand (e.g., prevalence of consumption), or related harms (e.g., hospitalizations and overdoses). The substances studied included heroin, cocaine, amphetamines, methamphetamine, ecstasy, synthetic opioids, and new psychoactive substances. Studies related to cannabis were excluded, as its production does not involve precursor chemicals. Only publications in English, Spanish, and Italian were considered.

A total of 11,289 search results were imported into Rayyan for initial duplicate removal. Titles and abstracts were then screened for relevance by two reviewers (SM and KSJ). Full-text papers were subsequently assessed for eligibility independently by the same two reviewers. Any disagreements were resolved through discussion or, if needed, consultation with a third reviewer (LG). Expert consultation identified four additional studies, one of which met the inclusion criteria after a detailed review.

Figure 1. PRISMA Flow Diagram Depicting the Study Selection Process for the Review



Eligibility Assessment

To ensure methodological rigor, we assessed whether studies met the minimum inclusion criteria established by the Cochrane Effective Practice and Organization of Care Group (EPOC). Studies were only included if they were randomized controlled trials, controlled clinical trials, controlled before-after studies, or interrupted time-series studies. For interrupted time-series studies, we required a clearly defined intervention point with a minimum of three data points both before and after the intervention. Studies that did not meet these criteria were excluded from the analysis.

Data Extraction

Study details were extracted using a standardized form covering study characteristics

(author, year, country, design), population demographics and substance use patterns, intervention type and implementation level, comparators, outcome measures, analysis methods, results and limitations. The extraction form was pilot tested on 5 studies, and data were extracted independently by two reviewers, with discrepancies resolved through consensus.

We chose a narrative synthesis because the studies varied significantly in both interventions and methodologies. Each precursor regulation targets different chemicals and involves a mix of rules on storage, sales, recipient eligibility, and operational conditions. Additionally, while some regulations control exports, others apply to national trade, retail, or wholesale markets.

The studies we reviewed also differed widely. They examined various locations, covered different time periods, assessed markets at different stages of drug trafficking growth, and used diverse outcome measures with varying follow-up intervals. This variability creates high statistical heterogeneity, making any summary measure (such as a meta-analysis) potentially misleading and violating the assumptions needed to combine effect sizes (Nicosia and Smart, 2024).

Attempting to aggregate these results could obscure important contextual factors, such as enforcement challenges and policy adaptations, which are crucial for understanding how precursor regulations work. A narrative review allows us to examine how different regulatory frameworks and contexts influence outcomes—without forcing inconsistent data into a single summary. This approach also accounts for variations in study quality, ensuring that each intervention's nuances are properly analyzed.

Given these factors, a narrative synthesis offers clearer insights into the uneven effects of precursor regulations than a meta-analysis would, making it the more appropriate approach for our review.

Risk of Bias Assessment

We used the EPOC Risk of Bias Tool to systematically evaluate the methodological limitations of included studies. Two reviewers (SM and KSJ) independently assessed each study, rating specific bias domains as low, unclear, or high risk. Any discrepancies were resolved through discussion, consulting a third reviewer (LG) if needed, or by reaching a consensus.

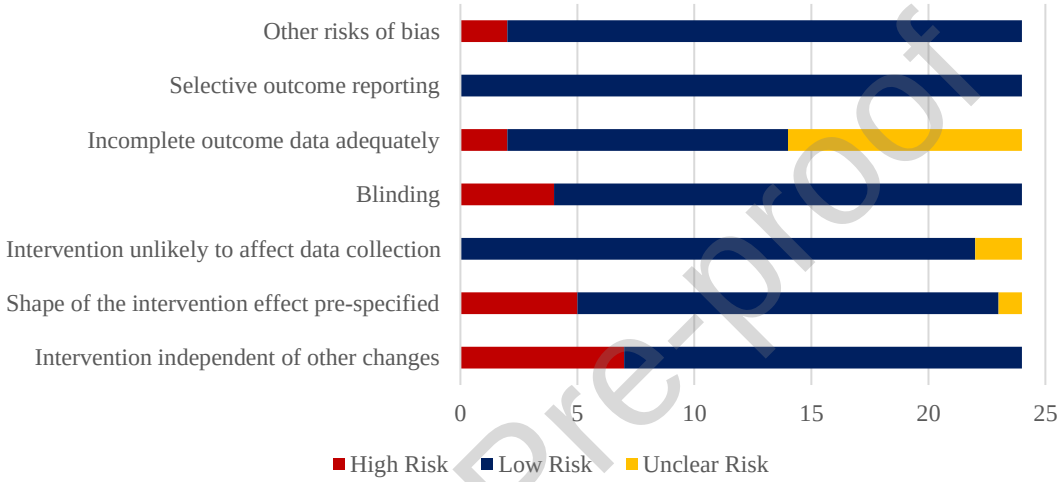
We assessed the risk of bias in studies using different criteria depending on whether they were ITS or CBA designs. Overall, the studies were judged to have a reasonably low risk of bias.

Figure 2 shows the coding across various dimensions for ITS studies, while Annex 3 provides detailed coding for each dimension of every CBA and ITS study. The supplementary material also provides detailed judgments and justifications for each bias criterion, along with the characteristics of the included studies.

The majority of ITS studies exhibit a low risk of bias across all dimensions. Specifically, this tool indicates low risk that the intervention influenced the data collection process, that outcomes were selectively reported, or that the shape of intervention effects lacked explanation. However, there are some dimensions where the risk of bias appears to be higher. One particularly relevant dimension for understanding the impact of precursor control is whether the intervention was independent of other changes. In 7 studies (27%), there was a high risk that external factors, such as unrelated policy changes or events, may have influenced the outcomes during the study period.

This is a long-standing and debated issue concerning ITS studies and an inherent limitation when studying changes in national policies. Some studies, however, go to greater lengths to investigate whether other factors may have influenced outcomes during the same period. These studies often include control groups and, in some cases, employ stronger research designs to minimize the potential impact of confounding factors. For example, d'Este (2021) and Freylejer and Orr (2023) use variation in the timing of state-specific restrictions on over-the-counter medications containing methamphetamine precursors.

Figure 2. Risk of Bias Using the EPOC Tool for Interrupted Time Series



Results

The final sample consisted of 26 studies (see Table 1). They were all written in English, published between 2003-2023, and were made up of journal articles (n=24), a government report (n=1) and a doctoral thesis (n=1). There were 2 study designs: Interrupted time series (n=24) and controlled before-after (n=2). The interventions were directed at 3 different substances: Methamphetamine (n=23), Cocaine (n=3) and Heroin (n=1); and were located in the USA (n=20), Canada (n=1), Mexico (n=1), Australia (n=3) and the Czech Republic (n=1).

The studies examined 11 different outcomes related to drug supply, use, and associated harms. Price was the most frequently used indicator, used in 8 different studies. Ten studies analyzed outcomes related to hospitalization, though these encompassed a variety of measures, including fatal and non-fatal intoxication, maternal and neonatal hospital stays, and general hospital admissions. Additionally, lab detection (n=6), drug seizures (n=3), and % d-methamphetamine exhibit (n=1) were used to indicate supply. Arrests (n=6), crime (n=1), toxicology (n=3) and past prevalence (n=1)

were used to indicate use. One study looked to see if regulation changed the route of administration (n=1).

Table 1: Characteristics of included studies

Characteristics of studies (n=26)	N	%
Publication year:		
2003-2005	2	8
2006-2010	7	27
2011-2015	10	38
2016-2020	5	19
2021-2023	2	8
Source:		
Journal article	24	92
Government report	1	4
Doctoral thesis	1	4
Language:		
English	26	100
Location:		
United States	20	77
Canada	1	4
Mexico	1	4
Australia	3	12
Czech Republic	1	4
Study design:		
Interrupted time-series	24	92
Controlled Before and After	2	8
Drug type:		
Methamphetamine	23	88
Heroin	1	4
Cocaine	3	12
Outcome measures:		
Price	8	31
Purity	5	19
Lab detection	6	23
Drug Seized (Heroin, Cocaine or Meth)	3	12

% d-methamphetamine exhibit	1	4
Arrests (inc. production, supply or possession)	6	23
Crime (Larceny, Burglary, or Assault)	1	4
Hospital care (Admissions, discharges, acute-care, non-fatal intoxication, treatment, maternal and neo-natal stays)	10	38
Toxicology (Emergency care, arrests, workplace testing)	3	12
Past prevalence (Month or Year)	1	4
Route of administration (Snorting, Smoking, Swallowing or Injecting)	1	4

Overview of Drug Precursor Control Regulations

There were 37 interventions in total, including 11 US federal laws and a law enforcement effort, 10 US state-level regulations, three Canadian regulations, five Mexican regulations and a law enforcement effort, a Czech Republic regulation, two Australian system rollouts, and three Australian regulations. Of these, 10 targeted wholesale sales, 25 targeted retail level sales and two were the resulting impact of a law enforcement effort (rogue company closures). Additionally, two targeted precursors for heroin, four for cocaine, and 33 for methamphetamine. For a detailed list and description of these interventions, see Annex 2.

There were seven US federal regulations which targeted wholesale distribution. The CDTA (1989) targeted heroin, cocaine and methamphetamine production and obliged wholesale providers to maintain records of sales of listed chemicals, which could be examined by law enforcement. The DCDCA (1995) revised regulations to increase the number of products included. The MCA (1996/1997) included combined products in the regulation and further tightened wholesale thresholds for methamphetamine precursors. The US Acetic anhydride mixture regulation (2005) targeted heroin and governed chemical mixtures which contained acetic anhydride. The US solvent regulation (1992), the MIBK (1995) and the US Sodium Permanganate Regulation (2006) all targeted cocaine production: the Solvent Regulation (1992) categorized sulfuric and hydrochloric acid as a list II chemical, the MIBK (1995) regulated Methyl isobutyl ketone under the Controlled Substances Act, and the Sodium Permanganate Regulation (2006) categorized Sodium Permangulate as a list II chemical. In 2005, police shut down a company illegally diverting chemicals to produce methamphetamines.

The remaining US federal interventions targeted retail level sales for methamphetamine; the DCDCA (1995) enhanced the reporting and enforcement process for essential chemicals by establishing limits on retail sales, and the MCA (1996) further tightened retail limits of combined products. The MAPA (2000) and CMEA (2006) phase 1 imposed purchase limits for precursors, and the CMEA (2006) phase 2 specified storage conditions and required details to be obtained from customers. All US state-level laws put conditions on the retail sale and purchase of pseudoephedrine, before the federal CMEA (2006) came into effect.

All remaining interventions targeted the production of methamphetamine. The Canadian Controlled Drugs and Substances Act (2003/2004) came out in three phases and regulated the producers, distributors and buyers of precursors and essential chemicals at a wholesale level. Mexico increased their regulation with two wholesale interventions around pseudoephedrine (2005), before banning the chemical in 2008. Additionally, the rogue pharmaceutical company closure (2007) disrupted the wholesale supply chain. The remaining two Mexican interventions targeted retail level sales. Phase 2 of the Pseudoephedrine regulation (2006) set restrictions on distribution and required mandatory reporting of sales, and the implementation of the Precursor Prescription Requirement (2007).

The only European country included in the systematic review was the Czech Republic, which rapidly tightened its retail level regulations for precursor chemicals. Lastly, Queensland, Australia implemented ‘Project Stop’ (2005/2007) which initiated a Linked Electronic Medication Recording System (LEMS) to record the sales of pseudoephedrine. The Pseudoephedrine regulation (2006) recategorized pseudoephedrine to pharmaceutical medication and the Pseudoephedrine rescheduling changes (2006) reclassified set doses to prescription only. Mandatory reporting of sales occurred in 2008.

Table 2. Reported Impacts of Precursor Regulations on Outcome Measures

Intervention	Illicit drug affected	Outcome measure	Location	Impact	Control	Study
US Chemical Diversion & Trafficking Act (CDTA 1989)	Methamphetamine	Hospital admission	California	-35%	NA	(Cunningham and Liu, 2003)
		Arrests	California	-44%	Decline in heroin and cocaine, but not for marijuana	(Cunningham and Liu, 2005)

			California	-21%[1]	NA	(Ponicki *et al.*, 2013)
		Hospital discharges	California	-50%[1]	NA	
		Purity	Continental US	-16.57p	Decline in heroin and cocaine purity.	(Cunningham, Liu and Callaghan, 2009)
		Price		$92.52	NA	
		Purity	Continental US	-40%	NA	(Cunningham, Liu and Callaghan, 2013)
	Heroin	Price	Continental US	93%	NA	
		Heroin Seized	Continental US	-27%	NA	
		Purity	Continental US	-4%	Decline for methamphetamine and heroin, but not for marijuana	
	Cocaine	Price	Continental US	36%	Increase for methamphetamine and heroin, but not for marijuana	(Cunningham, Callaghan and Liu, 2015)
		Cocaine Seized	Continental US	-28%	Decline for methamphetamine and heroin, but not for marijuana	
		Hospital admission	California	-48%	NA	(Cunningham and Liu, 2003)
			Arizona	-71%	NA	
			Nevada	-52%	NA	
		Arrests	California	-51%	No change for marijuana, heroin, or cocaine	(Cunningham and Liu, 2005)
		Hospital Discharges	California	-52%	NA	(Ponicki *et al.*, 2013)
			California	-62%	NA	
		Voluntary Treatment admission	California	-39%	No change for alcohol, heroin, or cocaine	(Cunningham and Liu, 2008)
US Domestic Chemical Diversion and Control Act (DCDCA 1995)	Methamphetamine	Route of administration: snorting	California	-50%	No change in route of heroin administration	
		Route of administration: Smoking	California	-43%	No change in route of heroin administration	(Cunningham, Liu and Muramoto, 2008)
		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	-67.91p	No change for heroin. Slight decrease for cocaine	(Cunningham, Liu and Callaghan, 2009)
		Price		$34.77	NA	
US Comprehensive Methamphetamine Control Act	Methamphetamine	Hospital admissions	California	-	NA	(Cunningham and Liu, 2003)
			Arizona	-	NA	
			Nevada	-	NA	

(MCA 1996) – Phase 1		Arrests	California	-	No change in marijuana, heroin, or cocaine	(Cunningham and Liu, 2005)
		Route of administration: Snorting		-	No change in route of heroin administration	
		Route of administration: Smoking	California	40%	No change in route of heroin administration	(Cunningham, Liu and Muramoto, 2008)
		Route of administration: Swallowing		-	No change in route of heroin administration	
		Route of administration: Injecting		-	No change in route of heroin administration	
		Purity	Continental US	-	No change in heroin or cocaine purity	(Cunningham, Liu and Callaghan, 2009)
		Price		-	NA	
		Hospital admission	California	-53%	NA	(Cunningham and Liu, 2003)
			Arizona	-25%	NA	
			Nevada	-77%	NA	
		Arrests	California	-60%	No change in cocaine, heroin, or marijuana	(Cunningham and Liu, 2005)
		Hospital discharges	California	-17%[3]	NA	(Ponicki *et al.*, 2013)
			California	-34%[3]	NA	
		Voluntary Treatment admission	California	-31%	No change in cocaine, heroin, or alcohol	(Cunningham and Liu, 2008)
US Comprehensive Methamphetamine Control Act (MCA 1997) – Phase 2	Methamphetamine		Texas, US	-	No change for cocaine, heroin, and alcohol admissions	(Cunningham *et al.*, 2010)
		Route of administration: snorting	California	-38%	Brief decline in number of heroin smokers	(Cunningham, Liu and Muramoto, 2008)
		Route of administration: Smoking		-	No change in route of heroin administration	
		Route of administration: Swallowing		-	No change in route of heroin administration	
		Route of administration: Injecting		-	No change in route of heroin administration	
		Purity	Continental US	-28.94p	No change for heroin or cocaine	(Cunningham, Liu and Callaghan, 2009)
		Price		$76.14	NA	
US Methamphetamine Anti-Proliferation Act (MAPA 2000)	Methamphetamine	Treatment admissions	State level (omitting California), US	-	NA	(Nonnemaker, Engelen and Shive, 2011)
		Meth Seized		-		
		Lab seizures		-		
		Price		-US$86		
				-	NA	

		Purity	Continental US	-	Increase in cocaine but not heroin	(Cunningham, Liu and Callaghan, 2009)
			State level (omitting California), US	9 % points	NA	(Nonnemaker, Engelen and Shive, 2011)
		Voluntary Treatment admission	Texas, US	-	Increase for heroin, cocaine, and alcohol	(Cunningham *et al.*, 2010)
US Combat Methamphetamine Epidemic Act (CMEA 04/2006) Phase 1	Methamphetamine	Lab Seizures	Oregon, USA	-	No change for nearby states. Idaho introduce precursor reg at the same time of Oregon	(Cunningham *et al.*, 2012)
			Mississippi, USA	-	No change for nearby states. Florida introduce precursor reg at the same time of Mississippi	
		Larceny	Continental US	3.2%	NA	(d'Este, 2021)
		Burglary		3%		
		Aggravated Assault		2.8%		
US Combat Methamphetamine Epidemic Act (CMEA 09/2006) - Phase 2	Methamphetamine	Lab seizures	Oregon, USA	-	No change for nearby states. Idaho introduce precursor reg at the same time of Oregon	(Cunningham *et al.*, 2012)
			Mississippi, USA	-	No change for nearby states. Florida introduce precursor reg at the same time of Mississippi	
US Acetic anhydride mixture regulation (2005)	Heroin	Purity	Continental US	-	NA	(Cunningham, Liu and Callaghan, 2013)
		Price	Continental US	-	NA	
		Heroin Seized	Continental US	-	NA	
US Solvent regulation (1992)	Cocaine	Purity	Continental US	-	No alterations for marijuana, heroin; methamphetamine changes due to targeted interventions	(Cunningham, Callaghan and Liu, 2015)
		Price	Continental US	-		
		Cocaine Seized	Continental US	-29%		
US Methyl isobutyl ketone regulation (1995 MIBK)	Cocaine	Purity	Continental US	-	No alterations for marijuana, heroin; methamphetamine changes due to targeted interventions	(Cunningham, Callaghan and Liu, 2015)
		Price	Continental US	25%		
		Cocaine Seized	Continental US	-		
US Sodium Permanganate	Cocaine	Purity	Continental US	-35%	No change to marijuana,	(Cunningham,

Regulation (2006)		Price	Continental US	100%	heroin; methamphetamine changes due to targeted interventions	Callaghan and Liu, 2015)
		Cocaine Seized	Continental US	-22%		
		Past year prevalence	US	-32%	No change to heroin and marijuana	(Cunningham, Liu and Callaghan, 2016)
		Past month prevalence	US	-29%		
		Maternal hospital stays	US	-221 hospital stays	NA	(Delcher *et al.*, 2017)
		Neonatal hospital stays	US	-128 hospital stays		
		Purity		-70 pp	NA	
		Price		$70		
		Hospital admissions		-50%	No change to marijuana, heroin, or cocaine. Slight increase to alcohol.	
US Rogue Company Closures (1995)	Methamphetamine	Treatment admissions	California, US	-35%	No change to other admissions	(Dobkin and Nicosia, 2009)
		Toxicology on arrests		-55%	No change to marijuana, heroin, or cocaine	
		Arrests		-50%	No change to cocaine or heroin. Increase in marijuana.	
Texas House Bill 164 (2005)	Methamphetamine	Voluntary treatment admission	Texas, US	-	Little/ No change for cocaine, heroin, or alcohol	(Cunningham *et al.*, 2010)
Oregon Store Regulation (2001) – Phase 1		Lab seizures	Oregon, USA	-	No change for Washington, California, and Nevada. Idaho introduce precursor reg at the same time of Oregon	(Cunningham *et al.*, 2012)
Oregon Store Regulation (2004)– Phase 2			Oregon, USA	-		
Oregon Store Regulation (2005) – Phase 3	Methamphetamine	Lab Seizures	Oregon, USA	-47%	No change for Washington, California, and Nevada. Idaho introduce precursor reg at the same time of Oregon	(Cunningham *et al.*, 2012)
Oregon Prescription Regulation (2006)		Lab seizures	Oregon, USA	-	No change for Washington, California, and Nevada. Idaho introduce precursor reg at the same time of Oregon	(Cunningham *et al.*, 2012)
Mississippi Store	Methamphetamine	Lab seizures	Mississippi, USA	-63.4%	No change for nearby states.	

Regulation (2005)					Florida introduce precursor reg at the same time of Mississippi	(Cunningham *et al.*, 2012)
Mississippi prescription regulation (2010)			Mississippi, USA	-50.2%		
			Mississippi, USA	-77%	NA	(Cunningham, Finlay and Stoecker, 2015)
		Price	Mississippi, USA	-		
Oklahoma House Bill (2004)	Methamphetamine	Urine drug screen	Oklahoma, USA	14-19%	No change to Barbiturates, Benzodiazepines, Cannabis, Cocaine or Opiates	(Brandenburg *et al.*, 2007)
		Larceny	39 US states	3.7%	NA	(d'Este, 2021)
		Burglary		3.2%		
		Aggravated assault		2.7%		
		Lab seizures	32 US states[2]	-65%	NA	(McBride *et al.*, 2011)
				-36%	NA	
US State-level law restricting pseudoephedrine-based medication (2004-2006)	Methamphetamine	Arrests	35 US states	-	NA	(Dobkin, Nicosia and Weinberg, 2014)
		Consumption		-	NA	
		Price	39 US states	-	NA	(Freylejer and Orr, 2023)[4]
				+ 30–35% (near border); + 40–55% (farthest from the border)	No change for cocaine	
		Purity	Continental US	+15.70p	No change for heroin or cocaine	(Cunningham, Liu and Callaghan, 2009)
Canadian Controlled Drugs and Substances Act (01/2003)– Phase 1	Methamphetamine	Acute-care hospital admission	Canada	-	No change for cocaine, heroin/opioids, alcohol	(Callaghan *et al.*, 2009)
		Voluntary Treatment admission	Texas, USA	-	Little/no change for cocaine, heroin, and alcohol admission	(Cunningham *et al.*, 2010)
Canadian Controlled Drugs and Substances Act	Methamphetamine	Purity	Continental US	+13.68p	No change for heroin or cocaine	(Cunningham, Liu and Callaghan, 2009)

(07/2003)– Phase 2		Acute-care hospital admission	Canada	20%	No change for cocaine, heroin/opioids, alcohol	(Callaghan *et al.*, 2009)
		Voluntary Treatment admission	Texas, USA	-	Little/no change for cocaine, heroin, and alcohol admission	(Cunningham *et al.*, 2010)
		Purity	Continental US	-13.87p	No change for heroin or cocaine	(Cunningham, Liu and Callaghan, 2009)
Canadian Controlled Drugs and Substances Act (01/2004)– Phase 3	Methamphetamine	Acute-care hospital admission	Canada	21%	No change for cocaine, heroin/opioids, alcohol	(Callaghan *et al.*, 2009)
		Voluntary Treatment admission	Texas, USA	-	Little/no change for cocaine, heroin, and alcohol admission	(Cunningham *et al.*, 2010)
Mexico Increases precursor control (1/2005)	Methamphetamine	% d-methamphetamine exhibits	Continental US	-62%	Little/no change for heroin, cocaine, and marijuana	(Cunningham *et al.*, 2013)
Mexican Pseudoephedrine regulation (11/2005)– Phase 1	Methamphetamine	Voluntary 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	Continental US	-	No change heroin and marijuana	(Cunningham, Liu and Callaghan, 2016)
		Past month prevalence	Continental US	-	No change heroin and marijuana	
Mexican Domestic Distribution Restriction (2/2006)- Phase 2	Methamphetamine	% d-methamphetamine exhibits	Continental US	-	Little/no change for heroin, cocaine, and marijuana	(Cunningham *et al.*, 2013)
Mexican Rogue company closure (2007)	Methamphetamine	Voluntary 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	Continental US	-35%	No change heroin and marijuana	(Cunningham, Liu and Callaghan, 2016)
		Past month prevalence	Continental US	-45%	No change heroin and marijuana	
		Voluntary Treatment admission	Texas, USA	-	Little/no change for cocaine, heroin, and alcohol admission	(Cunningham *et al.*, 2010)
Mexican Precursor Prescription Requirement (09/2007)	Methamphetamine	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)
		Voluntary Treatment admission	Texas, USA	-	Little/no change for cocaine, heroin, and alcohol admission	(Cunningham *et al.*, 2010)
Mexican Precursors ban (2008)	Methamphetamine	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)
		Individual arrests		-		
Czech Republic Precursor Regulation (2009)	Methamphetamine	Meth related non-fatal intoxication requiring hospital admission	Czech Republic	-	No change for heroin	(Petruželka and Barták, 2020)
Australian 'Project STOP' (2005)	Methamphetamine	Detected clandestine laboratories (rate)	Queensland, Australia	−1.13 per 100,000 (Jan 2004 – Jul 2008) 8.62 per 100,000 (Jul 2008 – Aug 2009)	NA	(Ferris *et al.*, 2016)

		Production (arrests)		-		
		Supply (arrests)		+88 arrests	NA	(Mazerolle *et al.*, 2017)
		Possession (arrests)		-		
		Treatment admissions		+32.66 admissions the following month	No change for Alcohol or cannabis	
Australian 'Project STOP' national rollout (2007)	Methamphetamine	Treatment admissions	Queensland, Australia	-	No change for Alcohol or cannabis	
Australian Pseudoephedrine regulatory changes (01/2006)	Methamphetamine	Treatment admissions	Queensland, Australia	-1.71 admissions per month for the next 29 months	No change for Alcohol or cannabis	(McGuffog, 2012)
Australian Pseudoephedrine rescheduling changes (04/2006)	Methamphetamine	Treatment admissions	Queensland, Australia	-	No change for Alcohol or cannabis	
Australian regulation requiring Mandatory reporting of pseudoephedrine sales (6/2008)	Methamphetamine	Treatment admissions	Queensland, Australia	+31.99 admissions that month, however its effect slowly declined	No change for Alcohol or cannabis	

[1] The study found that the 1989 CDTA had lagged effects, with reductions of 48% in arrests and 44% in hospital discharges occurring in the year following its implementation. [2] This is the combined effect of state and federal policy changes, with state policies reducing STL seizures by 48% and federal purchase quantity limits reducing them by 33%, assuming the effects are multiplicative because the policies impact STL seizures simultaneously but independently. [3] The study also found that the 1997 MCA had lagged effects, with an additional year of implementation resulting in reductions of approximately 21% in arrests and 33% in hospital discharges. [4] The study finds that precursor controls increased domestic production costs by 114%–190%. Following these controls, import shares rose from around 60% to 75–85% in areas closest to the border and from 40% to 60–75% in areas farthest from the southwest border. Substitution toward Mexican-produced methamphetamine reduced the impact of precursor controls on methamphetamine prices by 62%–83% compared to a scenario without import substitution.

Impact by Intervention

Of the 37 interventions examined, 14 were effective and 23 were ineffective. Among the effective interventions, 5 targeted wholesale markets, 7 focused on retail sales, and 2 measured the impact of shutting down rogue companies. One effective intervention

targeted heroin, cocaine and methamphetamine; one specifically targeted cocaine; and 12 specifically targeted methamphetamine. Four were US state level regulation, five were US state level regulation, four were Mexican regulation, and one was Australian regulation. No effective interventions were measured in Canada or the Czech Republic. See Table 2 for a detailed breakdown of outcomes by intervention type.

Heroin

CDTA (1989) had a significant impact in reducing heroin related outcomes. Following its implementation, heroin prices increased by 93%, while purity and seizures decreased by 40% and 27%, respectively, indicating a reduced supply that lasted 2–5 years (Cunningham, Liu and Callaghan, 2013). Because U.S. heroin mainly came from Mexico and Southeast Asia, the authors suggest that production in these regions was likely affected.

In contrast, the U.S. acetic anhydride mixture regulation of 2005 was ineffective in reducing seizures or influencing purity and price, suggesting it had no impact on heroin supply (Cunningham, Liu and Callaghan, 2013). This may be because acetic anhydride was not commonly used in commercial mixtures at that time. The authors suggest that the regulation might have helped prevent future misuse of acetic anhydride in mixtures used to produce heroin (Cunningham, Liu and Callaghan, 2013).

Cocaine

As with heroin, the CDTA of 1989 was highly effective in reducing cocaine-related outcomes by regulating potassium permanganate. Following its implementation, cocaine prices increased by 36%, while purity and seizures decreased by 4% and 28%, respectively, indicating a reduced supply that lasted 1–2 years (Cunningham, Callaghan and Liu, 2015).

The U.S. solvent regulation of 1992 and the MIBK regulation of 1995 showed significant effects, but only in one outcome each. The solvent regulation led to a 29% decrease in seizures, while the MIBK regulation resulted in a 25% increase in price (Cunningham, Callaghan and Liu, 2015).

Sodium permanganate, a direct substitute for potassium permanganate, saw a surge in U.S. production and exports in the early 2000s, just before the 2006 U.S. Sodium Permanganate Regulation (Cunningham, Callaghan and Liu, 2015). This may

explain why the 2006 regulation had such a strong impact. The regulation reduced seizures by 22% (Cunningham, Callaghan and Liu, 2015), past-year prevalence by 32%, past-month prevalence by 29% (Cunningham, Liu and Callaghan, 2016), and maternal and neonatal hospital stays (Delcher *et al.*, 2017). Notably, these reductions showed little to no recovery even after the data collection periods of 5 years (Cunningham, Callaghan and Liu, 2015), 7 years (Delcher *et al.*, 2017), and 8 years (Cunningham, Liu and Callaghan, 2016).

Methamphetamines

United States of America

The CDTA of 1989 was consistently effective in reducing methamphetamine-related outcomes in California. Hospital admissions dropped by 35% (Cunningham and Liu, 2003), while hospital discharges and arrests saw significant declines, with arrests decreasing by 44% (Ponicki *et al.*, 2013). These outcomes indicate a reduction in methamphetamine use lasting up to three years.

Across the continental U.S., methamphetamine prices increased, and purity decreased by 16.57 points (Cunningham, Liu and Callaghan, 2009), suggesting an overall reduction in supply. However, purity began to resurge three years later and surpassed 80% of pre-intervention levels within five years (Cunningham, Liu and Callaghan, 2009).

The DCDCA (1995) was consistently effective in reducing methamphetamine-related outcomes in California, Arizona and Nevada. Hospital admissions decreased by 48–71%, though they began to resurge after six months (Cunningham and Liu, 2003). Voluntary treatment admissions dropped by 39%, with the effect lasting two years (Cunningham and Liu, 2008). Hospital discharges and arrests also declined significantly (Cunningham and Liu, 2005; Ponicki *et al.*, 2013), with these reductions lasting for up to two years (Cunningham and Liu, 2005). All measured routes of administration decreased by 26–50% (Cunningham, Liu and Muramoto, 2008), reflecting an overall reduction in use. Injecting, swallowing, and snorting routes remained at lower levels even nine years later, at the end of the study period.

Evidence also suggests that the DCDCA (1995) was effective across the continental U.S. Although the effect was brief, prices increased by $34, while purity

dropped by approximately 68 percentage points (Cunningham, Liu and Callaghan, 2009).

The 1995 closure of a company involved in diverting chemicals for methamphetamine production was effective in reducing meth-related outcomes in California. Following the closure, prices increased, and purity decreased (Dobkin and Nicosia, 2009). Meth-related hospital admissions dropped by 50%, treatment admissions declined by 35%, arrests fell by 50%, and positive toxicology results among arrests decreased by 55% (Dobkin and Nicosia, 2009). While the price increase lasted only four months, purity, hospital admissions, treatment admissions, and arrests returned to near pre-intervention levels within 18 months (Dobkin and Nicosia, 2009).

The MCA (1996) phase 1 was ineffective at reducing methamphetamine outcomes for hospital admissions, arrests, price, and purity (Cunningham and Liu, 2003, 2005; Cunningham, Liu and Callaghan, 2009). This may be due to the legislation regulating products which were not widely used by large-scale producers. Additionally, route of admission saw a significant increase in smoking by 40% (Cunningham, Liu and Muramoto, 2008). The authors suggest that this rise in smoking, historically linked to Mexican methamphetamine production, reflected the growing prevalence of Mexican meth in the United States.

The MCA (1997) Phase 2 was effective in reducing methamphetamine-related outcomes. Hospital admissions in California, Arizona, and Nevada dropped by 25–77%, with a resurgence after one year, though levels remained below pre-intervention levels even eight years later (Cunningham and Liu, 2003). Hospital discharges and arrests also declined significantly (Cunningham and Liu, 2005; Ponicki *et al.*, 2013) with a partial rebound in arrests after four years in California (Cunningham and Liu, 2005). Supporting this, methamphetamine prices increased, and purity decreased by 28.94 points across the entire continental U.S. (Cunningham, Liu and Callaghan, 2009). In California, voluntary treatment admissions were found to decline by 31% lasting 4 years (Cunningham and Liu, 2008), however, no effect was found in Texas (Cunningham *et al.*, 2010). Authors suggest this may be due to the low numbers of admissions in Texas prior to the intervention.

The MAPA (2000) failed to reduce methamphetamine outcomes, showing no impact on treatment admissions, voluntary admissions, meth seizures, lab seizures, price, or purity (Cunningham, Liu and Callaghan, 2009; Cunningham *et al.*, 2010; Nonnemaker, Engelen and Shive, 2011). One study went further (Nonnemaker, Engelen

and Shive, 2011), showing that this regulation was actually linked to a significant increase in methamphetamine purity and a decrease in price.

The CMEA (2006) was similarly ineffective. Lab seizures showed no change after the regulation was implemented (Cunningham *et al.*, 2012), and one study reported a modest but significant increase in crime (d'Este, 2021). For both the CMEA (2006) and MAPA (2000), their ineffectiveness is largely attributed to their focus on small-scale producers and the rise in meth imports from Mexico (Nonnemaker, Engelen and Shive, 2011; Cunningham *et al.*, 2012).

State-level laws showed mixed effectiveness in reducing methamphetamine-related outcomes. Texas's house bill had no effect on meth-related outcomes (Cunningham *et al.*, 2010), and Oklahoma's house bill led to a 14–19% increase in positive urine drug screens (Brandenburg *et al.*, 2007). The Oregon Store Regulation (Phase 3, 2005) and the Mississippi Store Regulation (2005) were both effective in reducing illicit labs, with lab seizures declining by 47% in Oregon and 63.4% in Mississippi (Cunningham *et al.*, 2012). Mississippi's Prescription Regulation (2010) led to a further reduction in lab seizures, ranging from 50.2% (Cunningham *et al.*, 2012) and 77% (Cunningham, Finlay and Stoecker, 2015). In contrast, Oregon's Prescription Regulation (2006) had no impact on lab-related outcomes, which the authors attribute to the already low number of lab seizures in Oregon before the legislation, compared to Mississippi (Cunningham *et al.*, 2012). Although the Mississippi Prescription Regulation (2010) reduced lab seizures, it had no effect on price, suggesting it did not impact methamphetamine availability (Cunningham, Finlay and Stoecker, 2015).

The grouped state-level laws (2004-2005) were also found to be effective at reducing labs seizures by 36% (Dobkin, Nicosia and Weinberg, 2014). Although there was a significant reduction in lab seizures, the same study found no difference in arrests, consumption or price, suggesting the availability of methamphetamine was unchanged. Freylejer and Orr's study (2023) explains this lack of impact on prices. They found that while precursor controls could have more than doubled meth prices, the U.S. market quickly adapted by shifting production to Mexico and increasing imports from there. As a result, price increases were minimal, with import substitution reducing the impact of precursor controls on prices by up to 83% in areas near the southern border.

Canada

The Canadian Controlled Drugs and Substances Act (2003/2004) was largely ineffective in Canada and the US (Callaghan *et al.*, 2009; Cunningham, Liu and Callaghan, 2009; Cunningham *et al.*, 2010). Unexpectedly, continental US saw purity increase by 15.7 points and 13.68 points in the first two phases (Callaghan *et al.*, 2009). However, purity declined by 13.87 points in the third phase, with median purity returning to 65-80% within two years (Callaghan *et al.*, 2009). Furthermore, acute-care hospital admissions in Canada increased 20% and 21% during the second two phases, which continued beyond the end of the series in 2005 (Callaghan *et al.*, 2009).

Mexico

Studies in this systematic review examined the impact of Mexican regulations on outcomes in both Mexico and the U.S. After Mexico introduced initial precursor control measures in 2005, U.S. law enforcement reported a 62% reduction in seizures of *d*-methamphetamine, the more potent isomer of methamphetamine (Cunningham *et al.*, 2013). This decline accelerated by an additional 40.5% following the implementation of the Pseudoephedrine Regulation in 2005 but saw a partial recovery in 2006 (Cunningham *et al.*, 2013).

The Pseudoephedrine Regulation (2005) also led to a 12% reduction in treatment admissions in Mexico and a 12% decline in voluntary treatment admissions in Texas, with effects lasting one year (Cunningham *et al.*, 2010). However, no significant changes were observed in past-year or past-month methamphetamine prevalence across the continental U.S. (Cunningham, Liu and Callaghan, 2016), suggesting the regulation had a stronger impact closer to the Mexico–U.S. border.

The Domestic Distribution Restriction (2006) was ineffective in reducing methamphetamine-related outcomes in the U.S. (Cunningham *et al.*, 2013), and no data is available for its impact in Mexico. Similarly, the Mexican Precursor Prescription Requirement (2007) was ineffective in both the U.S. and Mexico (Cunningham *et al.*, 2010, 2013). Its follow-up intervention, the Precursor Ban (2008), also showed no impact on methamphetamine outcomes in the U.S. (26, 27). In Mexico, the precursor ban was associated with a decline in treatment admission of 15%, with the effect lasting until the end of the series in 2009 (Cunningham *et al.*, 2010).

The closure of a rogue pharmaceutical company in Mexico (2007) led to significant reductions in methamphetamine-related outcomes in Mexico, Texas, and the continental U.S. In Mexico, treatment admissions dropped by 56%, while voluntary

treatment admissions in Texas decreased by 48%, with both effects lasting until 2008 (Cunningham *et al.*, 2010). In the U.S., *d*-methamphetamine seizures fell by 26.6%, with partial recovery in 2008 but effects persisting until 2011 (Cunningham *et al.*, 2013). Past-year prevalence in the U.S. declined by 35%, and past-month prevalence dropped by 45%. Although partial recovery was noted in 2013, these effects lasted beyond the study period, ending in 2014 (Cunningham, Liu and Callaghan, 2016).

Czech Republic

One study looked at the interventions implemented within the Czech Republic (Petruželka and Barták, 2020). Regulations of methamphetamine precursor chemicals were rapidly tightened; however, this was ineffective at reducing individual arrests and non-fatal intoxication requiring admission. The authors suggest this failure was due to trafficking shifting to more organized criminal groups, which sourced the necessary precursors from neighboring countries that had not tightened their access to these chemicals.

Australia

Project Stop, introduced in Queensland, Australia, in 2005, reported inconsistent results in reducing methamphetamine related outcomes. Lab detections showed a stable but declining trend during the initial phase of implementation. However, there was a significant increase once 90% of pharmacies enrolled in the project, followed by a stabilization in the trend (Ferris *et al.*, 2016). In contrast, Mazerolle and colleagues found no significant changes in production-related incidents (Mazerolle *et al.*, 2017).

Despite minimal changes in production, arrests for supply significantly increased for at least one year, and treatment admissions rose sharply for two months following the intervention (Mazerolle *et al.*, 2017). This increase in treatment admissions persisted until the implementation of the Pseudoephedrine Regulation (2006), after which admissions declined significantly for the next 2.5 years (McGuffog, 2012). However, mandatory reporting of sales in 2008 triggered a resurgence in treatment admissions, lasting until the end of the series the following year (McGuffog, 2012). No change in treatment admissions was observed following the rescheduling changes in 2006, but the proximity of this intervention to the 2006 regulatory changes

makes it difficult to distinguish their individual effects. The limited impact of Project Stop on production was attributed to changes in meth-cooking methods, shifts in police practices, an increase in the number of small clandestine labs, and—perhaps most importantly—the importation of methamphetamine from other jurisdictions (Ferris *et al.*, 2016), including high-quality crystal meth from Asia (Roche, 2017).

Discussion

This systematic review addresses a long-debated issue in drug policy: supply-side interventions can effectively disrupt illicit drug markets. Some of the most notable interventions include the CDTA of 1989, the DCDCA of 1995, the U.S. Sodium Permanganate Regulation of 2006, and the closure of two rogue companies in 1995 and 2007. The results are consistent across different time periods, substances, and authors.

The scale of these changes is striking, yet it is confirmed by multiple measures and studies. Drug prices doubled, hospital admissions fell by half, and reported drug use declined by a third. There is no evidence of substitution into other drugs.

The longevity of these effects is striking too, although it varies considerably. For cocaine, effects ranged from 1-2 years following the 1989 CDTA to at least seven years post-2006 U.S. Sodium Permanganate Regulation (Cunningham, Callaghan and Liu, 2015; Cunningham, Liu and Callaghan, 2016; Delcher et al., 2017). For heroin, the 1989 CDTA produced disruptions lasting 2–5 years (Cunningham, Liu and Callaghan, 2013). In contrast, methamphetamine interventions typically showed shorter-lasting effects of 4 months to max 2 years (Cunningham and Liu, 2003; Dobkin and Nicosia, 2009; Cunningham, Liu and Callaghan, 2016).

Methamphetamine likely rebounds more quickly due to its adaptability. Producers can switch to alternative synthesis methods or substitute different precursor chemicals, and they can easily relocate their operations. In contrast, heroin and cocaine manufacturing is less flexible: production sites cannot be as readily moved, and there are not as many viable chemical substitutes. This rigidity helps explain why crackdowns on those drugs tend to have more sustained effects. Still, two points remain clear. First, no intervention is permanent; markets eventually adjust. Second, even a temporary disruption can reduce drug-related harm, because its impact—though not everlasting—can be substantial.

These successful interventions share one key factor: they removed a critical ingredient for producing methamphetamine, cocaine, and heroin. This was done by either restricting access to precursors through stricter regulations or shutting down companies diverting chemicals to illegal drug production. In both cases, these actions caused at least temporary disruptions—until traffickers adapted by developing new methods to synthesize the drugs or sourcing chemicals from other suppliers. This is good news for drug policy makers.

There is, however, some bad news: in certain cases, precursor controls failed. Still, these failures offer valuable lessons for improving future policies. A common issue seems to be poor targeting. Regulations often focused on chemicals not used in drug production, overlooked key precursor sources, or allowed traffickers to source precursors elsewhere—undermining their effectiveness.

Some regulations focused on chemicals not actually used in making illicit drugs and had little impact on drug markets. For example, the 2005 U.S. regulation on acetic anhydride mixtures (over 20% concentration) caused no market changes. In contrast, the 1989 CDTA, which targeted pure acetic anhydride, significantly disrupted the heroin market (Cunningham, Liu and Callaghan, 2013). Similarly, later solvent regulations expanded the list of controlled chemicals, including those with sulfuric and hydrochloric acid, but were far less effective than the focused approach of the 1989 CDTA.

These regulations may not have impacted the market, but they might have anticipated future shifts. Illicit producers typically relied on pure acetic anhydride, not mixtures. However, when pure acetic anhydride became scarce, mixtures could have served as a fallback option. By restricting mixtures, the regulation may have eliminated this alternative and prevented future adaptations.

Interventions targeting retail sales had little impact. These measures focused on regulating the purchase and storage of medications containing ephedrine or pseudoephedrine in pharmacies. In North America, they disrupted small-scale production, shown by fewer lab detections and seizures, but had no broader effect on indicators like price or purity (Dobkin, Nicosia and Weinberg, 2014; Cunningham, Finlay and Stoecker, 2015). Large-scale production remained unaffected, as it does not rely on local pharmacies for ingredients. In Australia, however, similar regulations were linked to changes in treatment admissions (McGuffog, 2012; Mazerolle *et al.*, 2017), suggesting small-scale labs played a different role there. These differences highlight

how context—such as production methods, distribution networks, and geographic displacement—influences the outcomes of interventions..

Context also matters because competing supply channels can undercut the impact of precursor regulations. Evidence from Europe, North America, and Australia shows a clear pattern: when domestic access to precursors is blocked, traffickers can adapt by sourcing them elsewhere. In Canada, regulations aimed at curbing meth production backfired, leading to an increase in methamphetamine purity in the U.S. as Mexican producers filled the gap (Callaghan *et al.*, 2009). Freylejer and Orr (2023) found that U.S. regulations doubled domestic methamphetamine production costs but triggered a surge in imports from Mexico, cutting the policy's effectiveness by 80% in border areas. A similar trend was observed in the Czech Republic, where precursor regulations failed to shrink the meth market and instead drove traffickers to source precursors from neighboring countries with weaker rules (Petruželka and Barták, 2020). Geographic displacement is particularly well-documented in the case of methamphetamine, but less so for precursor controls targeting cocaine and heroin. These appear to be less adaptable, which may help explain the longer-lasting disruptions observed following regulation.

Limitations

Like any systematic review, this study has some limitations. The first relates to the search strategy. Although we followed a rigorous search protocol, we may have missed some studies. Research published in the grey literature or in languages other than English faced a higher risk of exclusion. To compensate for this, we searched 13 different databases, consulted experts in the field, and reviewed relevant organizations' publications.

Second, 77% of the studies (n = 20) were conducted in the United States, raising questions about whether our findings generalize to regions with different market structures, regulatory frameworks, and enforcement capacities. For example, retail-level methamphetamine precursor controls have produced markedly different outcomes in the U.S. versus Australia, demonstrating how regional context can fundamentally shape effectiveness. We should not assume precursor controls work the same way everywhere.

Third, the evidence base is heavily skewed toward methamphetamine precursor controls, which account for 88% of the included studies. There are hints that cocaine

and heroin regulations might have an even broader impact, but the evidence for these substances remain too sparse for firm conclusions. Crucially, no studies meeting our inclusion criteria address fentanyl or other synthetic opioids. And since geographic generalizability cannot be assumed, neither can the effectiveness of precursor controls be taken as uniform across all substances.

A fourth concern relates to evidence quality and potential confounding by concurrent interventions. To address this, we included only studies meeting the Cochrane EPOC Group's minimum design criteria and then applied the EPOC Risk of Bias Tool to evaluate each study's methodological rigour. This approach gives us a reasonable degree of confidence that observed changes are largely attributable to the interventions. However, we cannot completely rule out the possibility that other unmeasured factors influenced the results.

A final limitation concerns the enforcement of these regulations. None of the reviewed studies discuss this issue in depth. Is market disruption driven solely by the *de jure* existence of the rules—by raising the effort required to obtain precursor chemicals—or does the intensity and duration of disruption depend on how heavily those regulations are enforced? For example, are the interventions that produce the most disruptive and durable effects also the ones subject to the strictest enforcement? Current research cannot answer these questions, yet understanding them is essential for determining when—and under what conditions—precursor regulations can be most effective.

Considerations for future research

First, nearly all the studies reviewed treat precursor regulations as single, unified actions. However, these regulations consist of multiple components. Some focus on the storage of chemicals, others on who can sell them, and others on keeping transaction records or setting conditions for sales. But which of these components actually affects drug supply? For example, is it the requirement to track all transactions? Is it allowing law enforcement to access business records and shut down suspicious imports or exports? Or is it a combination of several measures?

Future research should explore how individual components impact drug supply. This would help policymakers design more effective regulations by focusing on the specific actions that have been proven to work.

Further research should confirm the results of some of these interventions. Some findings reported here are truly remarkable, both in their impact and duration — described as "unprecedented and wholly unanticipated"(Caulkins, 2015, p. 110). However, as Carl Sagan famously said: extraordinary claims require extraordinary evidence. We propose two research directions to help provide that evidence.

First, time series analysis should be conducted in other countries. This would help diversify the sample and improve our understanding of how contextual factors, such as geography and policy environments, shape outcomes. More importantly, it could help corroborate or refute claims about the impact of certain regulations. For example, every country in the world imports cocaine from South America. If sodium permanganate regulations work as claimed (Cunningham, Callaghan and Liu, 2015), we should expect to see similar disruptions in those countries as well.

Second, diversifying the evidence is key to understanding how precursor controls disrupt drug markets. Future studies — and possibly systematic reviews — should focus more on qualitative evidence to explore *how* regulating key chemicals affects criminal groups involved in drug production (Bouchard and Ponce, 2024). How do these groups learn about shortages? How do they adapt their operations? Where do they find alternative sources of precursors? These are the questions this research can help answer.

Lastly, regulating precursors will be increasingly challenging. Most interventions discussed here are outdated, with the most recent dating back to 2010. In the past 15 years, innovations in the chemical industry — particularly the rise of pre-precursors and designer precursors — have made it harder to control substances used in drug production. Pre-precursors are chemicals used to create drug precursors. For example, phenylacetic acid can be used to produce phenyl-2-propanone (P2P), a key ingredient in methamphetamine. Designer precursors are purposefully created to bypass regulations and often have no legitimate use. For instance, alpha-phenylacetoacetonitrile can be easily converted into P2P and was specifically designed to avoid P2P restrictions.

Future research should investigate the impact of recent precursor policies on drug markets. It is important to know if these regulations can still disrupt drug markets despite the rise of pre-precursors and designer precursors.

Conclusions

Precursor regulation can reduce drug supply, use, and harms. Compared to previous reviews (McKetin *et al.*, 2011), our review more than doubles the number of included studies and interventions, incorporates recent evidence on heroin and cocaine, covers additional countries, integrates new indicators, and evaluates newer regulatory measures.

Precursor regulations can be effective but are not a universal solution. Their success depends on how they are designed and where they are applied. Policymakers must consider local drug market structures, including production methods, operation scale, and supply channels. They should also anticipate potential displacement effects, particularly in regions with porous borders where regulations might shift precursor sourcing to neighbouring areas. Coordinating regulations across jurisdictions helps minimize such displacement. Additionally, the availability of alternative chemicals that could replace regulated precursors must be considered.

While there is reason for optimism, maintaining the effectiveness of precursor regulations may become challenging due to emerging trends like pre-precursors, designer precursors, easier chemical sourcing, and today's fast-moving global market.

Authorship contribution statement

LG: Writing – review & editing, Writing – original draft, Supervision, Conceptualization, Funding acquisition, Investigation. KSJ: Writing – review & editing, Writing – original draft, Formal analysis, Data curation, Methodology, Investigation. SM: Writing – review & editing, Writing – original draft, Formal analysis, Data curation, Methodology, Investigation

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Declaration of Interests

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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Declaration of Interests

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Highlights

- This review examines how precursor control affects illicit drug markets.
- Some controls show remarkable impact, with effects lasting months to several years.
- Some failed by targeting small supply or enabling supplier adaptation.