UNIVERSITÉ DE LILLE

FACULTÉ DE MÉDECINE HENRI WAREMBOURG

Année : 2024

THÈSE POUR LE DIPLÔME D'ÉTAT

DE DOCTEUR EN MÉDECINE

Epidémiologie des intoxications médicamenteuses et domestiques : analyse de la base CIGUE du Centre Antipoison de Lille

Présentée et soutenue publiquement le 25/06/2024 à 18h00
au Pôle Formation
par Harlan MOLHO

_____

JURY
Président :
Monsieur le Professeur Emmanuel CHAZARD
Assesseurs :
Monsieur le Docteur Matthieu CALAFIORE
Directeurs de thèse :
Monsieur le Professeur Emmanuel CHAZARD
Monsieur le Docteur Ramy AZZOUZ

_____

Avertissement

La Faculté n’entend donner aucune approbation aux opinions émises dans les thèses : celles-ci sont propres à leurs auteurs.

Sigles

AAPC	American Association of Poison Centers
ARS	Agence Régionale de Santé
ARSENIC	Système d'Aide à la Réponse et au Suivi des EmpoisonnemeNts et Intoxications au Centre antipoison
ANSES	Agence Nationale de Sécurité Sanitaire de l'alimentation, de l'environnement et du travail
ANSM	Agence Nationale de Sécurité du Médicament
ASPF	Agence Santé Publique France
BNPC	Banque Nationale des Produits et des Compositions
CAPTV ou CAP	Centre Antipoison et de Toxicovigilance
CIGUE	Centrale d'Informations et de Gestion en Urgences des Empoisonnements
CNIL	Commission Nationale de l'Informatique et des Libertés
DGS	Direction Générale de Santé
INVS	Institut National de Veille Sanitaire (remplacé en 2016 par l'Agence National de Santé Publique)
PSS	Poisoning Severity Score
SAMU	Service d'Aide Médicale Urgente
SICAP	Le Système d'Information des Centres AntiPoison et de toxicovigilance
WHO	*World Health Organization* (voir OMS)

Sommaire

Préambule

Le travail scientifique présenté dans cette thèse de médecine fera l'objet d'une publication d'article international en anglais. Il suit le plan suivant :

- Une introduction longue en Français, qui poursuit deux objectifs : présenter le contexte médical avec une orientation principalement pédagogique, et présenter le contexte scientifique et l'objectif, comme le fait également l'introduction de l'article en anglais
- L'article en Anglais, tel qu'il sera soumis à une revue scientifique internationale. Cet article suit le plan classique, dans le format imposé par le journal (introduction, matériel et méthodes, résultats, discussion)
- Une conclusion en Français

Le document est structuré ainsi en application de la circulaire Toubon[1].

Les références présentées en fin de document, ainsi que les listes de figures et tables, résultent de la fusion des parties en anglais et en français. La numérotation est donc incrémentée dans l'ensemble du document, que les parties soient anglophones ou francophones.

[1] Circulaire du 19 mars 1996 concernant l'application de la loi no 94-665 du 4 août 1994 relative à l'emploi de la langue française. JORF n°68 du 20 mars 1996 page 4258. NOR: PRMX9601403C

Introduction

1 Rôle et Organisation des Centres Antipoison et Toxicovigilance en France

1.1 Réseaux de Vigilances Français en Santé

La présente partie traite tout d'abord du problème plus général de l'organisation des vigilances en France. Comme nous l'évoquerons par la suite, les Centres Antipoison et de Toxicovigilance (CAPTV) s'intègrent dans le volet « toxicovigilance », que nous définirons préalablement. Ces centres sont couramment appelés CAP, centres antipoison.

1.1.1 Définition et missions des réseaux de vigilance

L'Agence Nationale de Sécurité des Médicaments (ANSM), sous la tutelle du Ministère de la Santé, assure la mise en œuvre des systèmes de vigilances relatifs aux produits sanitaire et d'hygiène corporelle destinés à l'humain. Leurs missions est définie par une veille sanitaire avec un processus continu de recueil, d'enregistrement, d'identification, de traitement, d'évaluation et d'investigation des événements indésirables liés à l'utilisation d'un produit. La déclaration pour un professionnel de santé ou un établissement de santé est obligatoire [1,2] :

« Tout professionnel ou établissement de santé ayant constaté ou suspecté la survenue d'un accident médical, d'une affection iatrogène, d'une infection nosocomiale ou d'un événement indésirable associé à un produit de santé doit en faire la déclaration à l'autorité administrative compétente » [2].

1.1.2 Objectifs des réseaux de vigilance

Les réseaux de vigilances ont pour objectif de surveiller les risques d'incidents ou d'effets indésirables de produits de santé après leur mise sur le marché. Le but est donc de garantir la sécurité du patient et l'efficacité des produits.

1.1.3 Les différents systèmes de vigilances

Il existe plusieurs réseaux de vigilances.

- **Biovigilance** concerne les éléments et produits issus du corps humain, à l'exclusion des gamètes et produits sanguins labiles ;
- **Cosmétovigilance** concerne l'ensemble des produits cosmétiques après la mise sur le marché ;
- **Hémovigilance** concerne les incidents et les effets indésirables chez les donneurs et receveurs de produits sanguins labiles ;
- **Matériovigilance** concerne les dispositifs médicaux après leurs mises sur le marché ;
- **Addictovigilance (ou Pharmacodépendance)** concerne les cas d'abus, de dépendance et d'usages détournés de substances psychoactives ;

- **Pharmacovigilance** a pour mission d'identifier, d'évaluer, d'établir une prévention de risque, potentiel ou avéré, d'effets indésirables des médicaments ;
- **Réactovigilance** concerne les incidents et les risques d'incidents liés à l'utilisation d'un dispositif médical de diagnostic *in vitro* ;
- **Vigilance des produits de tatouage** concerne l'ensemble des produits de tatouage après leur mise sur le marché ;
- **Toxicovigilance** fait l'objet du paragraphe suivant.

1.2 La Toxicovigilance

1.2.1 Définition et Mission

La toxicovigilance [3] est un système de vigilance sous la direction de l'Agence Nationale de Sécurité Sanitaire de l'alimentation, de l'environnement et du travail (ANSES) [4].

Elle a pour objet la surveillance des effets toxiques pour l'homme d'un produit, d'une substance ou d'une pollution, afin de mettre en œuvre des actions d'alerte, de prévention et d'information. Elle implique tout xénobiotique susceptible de provoquer des effets néfastes pour la santé [3].

Elle comporte :

- **Le signalement** par les professionnels de santé et les organismes de toute information relative aux cas d'intoxications aiguës ou chroniques et aux effets toxiques potentiels ou avérés résultant de produits ou de substances naturelles ou de synthèse ou de situations de pollution, à l'exception de celles relevant de systèmes nationaux particuliers de vigilance, notamment celui de pharmacovigilance ;
- **L'expertise, l'enregistrement et l'exploitation** de ces informations scientifiques et statistiques ainsi que de celles détenues par l'organisme ;
- **La réalisation et le suivi d'études ou de travaux** dans le domaine de la toxicité pour l'homme, d'un produit, d'une substance ou d'une pollution [3].

1.2.2 Organisation du Réseau National de Toxicovigilance

Depuis le 20/10/2004, la Direction Générale de Santé (DGS) a confié à l'Institut National de Veille Sanitaire (remplacé en 2016 par l'Agence Santé Publique France) d'animer et de coordonner le réseau national de toxicovigilance. En 2016, cette mission est déléguée à l'ANSES [4].

Le Comité de Coordination de Toxicovigilance est créé en juin 2005 avec plusieurs missions. Il est chargé de répondre aux saisines spécifiques du Ministère de la Santé ou d'autres autorités de santé publique. Il coordonne les investigations des alertes générés par les centres antipoison ou d'autres systèmes de surveillance. Il fournit une expertise en toxicologie clinique et contribue au suivi après la mise sur le marché de nouveaux produits, y compris les médicaments [3].

1.2.3 Organisation loco-régionale de Toxicovigilance

Le réseau loco-régionale est organisé par de multiples acteurs parmi lesquels on retrouve les professionnels de santé (ambulatoires ou hospitaliers), le grand public, les industriels et les CAPTV.

Les industriels participent en rédigeant systématiquement une fiche de sécurité ou d'information pour les produits qu'ils commercialisent. Cette fiche, avec la composition exacte du produit, est par la suite renseignée dans la banque nationale des produits et compositions (BNPC) [5].

Il existe 8 CAPTV en France métropolitaine et 2 dispositifs de toxicovigilance aux Antilles et à la Réunion (Figure 1). Ils ont pour missions [6] :

- De suivre l'évolution des intoxications pour lesquelles ils ont été consultés et de recueillir à leur sujet toutes les données utiles (circonstances, causes, gravité, imputabilité) ;
- De procéder à la collecte d'informations sur les autres cas d'intoxications qui se sont produits dans leur zone d'intervention ;
- D'alerter les services du ministère de la santé chargé et les autres services compétents, notamment ceux qui sont chargés de la consommation et de la répression des fraudes ;
- D'expertise toxicologique auprès des autorités administratives et des instances consultatives ;

Figure 1. Carte des Centres Antipoison français

2 Le CAP de Lille

2.1 Historique

Le premier centre antipoison fut créé aux Etats-Unis en 1953, à Chicago, par des pédiatres et des réanimateurs. En France, le premier CAP fut créé à l'hôpital Fernand Widal à Paris.

En 1964, à Lille, le Pr. Furon, débute l'élaboration d'un fichier toxicologique. En 1973, ce CAP sera relocalisé dans le nouveau service de réanimation de l'hôpital A. Calmette, puis en 1980 au second étage de l'Aile Est de l'hôpital devant un besoin d'espace pouvant contenir la totalité des archives.

Devant une croissance rapide des données et une nécessité à un accès en urgence aux informations, un système d'informatisation des données devient indispensable et en 1987, ARSENIC (système d'Aide à la Réponse et au Suivi des EmpoisonnemeNts et Intoxications au Centre antipoison) est développé par une équipe de médecins du CAP de Lille et d'informaticiens du CHU de Lille.

En 1995, une deuxième application est développée dans le cadre de traitements de données : CIGUE (Centrale d'Informations et de Gestion en Urgence des Empoisonnements). Elle est rapidement déployée au CHU de Lille puis dans la région Nord Pas de Calais.

En 1999, les deux applications fusionnent sous le nom de CIGUE [7].

2.2 Activité médicale

Le CAP de Lille est un service médical du Centre Hospitalier Universitaire de Lille. Son aire géographique est composée des Hauts de France. Il dessert une population d'environ 6 millions d'habitants [8]. Son fonctionnement est organisé autour de deux unités fonctionnelles de Réponse Téléphonique (24h/24h) et de Toxicovigilance [9,10].

Il ne possède pas d'unité de soins pour intoxiqués ni d'unité de consultation, ni d'un laboratoire de Toxicologie Analytique.

2.2.1 La réponse téléphonique

Le CAPTV de Lille est chargé de répondre, notamment en cas d'urgence, à toute demande d'évaluation des risques et à toute demande d'avis ou de conseil concernant le diagnostic, le pronostic et le traitement des intoxications humaines, accidentelles ou volontaires, individuelles ou collectives, aigues ou non, provoquées par tout produit d'origine naturelle ou de synthèse, disponibles sur le marché ou présent dans l'environnement [9,10].

2.2.2 L'activité documentaire spécialisée

Il possède une base de données informatisée CIGUE, permettant la consultation en temps réel des protocoles thérapeutiques nécessaires à la prise en charge des intoxiqués. Ces protocoles sont mis à jour quotidiennement par l'équipe médicale. Pour cette mise à jour, elle exploite les cas cliniques et elle dispose d'un fond documentaire (revues, livres, bases de données) [9,10].

2.2.3 Le suivi médical

L'équipe médicale assure un suivi médical de tous les cas d'intoxications humaines avérées ou présumées, afin de suivre l'évolution des intoxications pour lesquelles il a été consulté et recueillent toutes les informations médicales nécessaires [9,10].

2.2.4 La Toxicovigilance

Il procède à la collecte d'informations sur les autres cas d'intoxications survenues dans sa zone géographique, en particulier en partenariat avec les correspondants de Toxicovigilance (Samu-Centre 15), les hôpitaux sentinelles et les médecins généralistes.

Il assure une correspondance avec le Centre Régional de Pharmacovigilance, pour les cas d'intoxications médicamenteuses ayant provoqué des effets indésirables graves [9–14].

2.2.5 L'activité d'alerte

A partir de ces appels téléphoniques pour intoxications et de ces informations collectées auprès de ces correspondants de Toxicovigilance, il assure une mission d'alerte auprès des services du Ministre de la Santé et des autres services compétents, notamment ceux qui sont chargés de la consommation et de la répression des fraudes. Il alerte également les Agences Régionales de Santé en cas de danger pour la santé publique [9,10,15–17].

2.2.6 L'activité d'information

Le CAP informe sur les risques toxiques pendant la grossesse et l'allaitement, et assure l'information médicale « Air Santé » au sein de son dispositif de surveillance de la qualité de l'air, en cas de dépassement des seuils de pollution atmosphériques dans la région Nord-Pas de Calais [9,10].

En raisons de ses spécialisations sur les problèmes de l'environnement [18,19], le CAP de Lille a été sollicité par le CAP de Berlin et de Londres pour entrer dans le réseau européen des centre d'information sur les agents tératogènes (ENTIS [20]).

2.2.7 L'activité d'expertise et d'évaluation de risque

Le CAP assure également une mission d'expertise auprès des autorités administratives et des instances consultatives. Il participe également, au plan national en cas de risque chimique et toxicologique majeur, mise en place par le ministre de la santé [9,10].

2.2.8 L'enseignement, la recherche, la formation, l'éducation

Le CAP participe à l'enseignement et à la recherche en Toxicologie Clinique et assure la formation de ses correspondants départementaux de Toxicovigilance (SAMU-CENTRE 15) [10].

Le CAP a également une mission de pédagogie. C'est dans ce cadre que sont accueillis des internes et étudiants de différentes spécialités et formations (interne de médecine générale, de médecine du travail, de pharmacie ; externe de médecine et de pharmacie ; étudiants ingénieurs en santé et en science des données).

Il assure l'éducation de la population par son site internet [9,10].

2.3 Rapport Annuel

Jusqu'en 2006 [9], le CAPTV de Lille publiait annuellement un rapport de son activité et des missions réalisées dans l'année, d'abord en format papier puis sur son site internet. Ces rapports n'ont jamais été traduits ou publiés au travers d'articles scientifiques, sur des bases de données telles que PubMed.

Ce rapport a toujours été succinct avec des critères très ciblés, choisis par les professionnels du CAPTV de Lille.

Il n'existe à ce jour, aucun rapport systématique avec des critères transposables, ni de publications épidémiologiques régulières. Pourtant il est indispensable de décrire et d'analyser régulièrement les données pour anticiper les tendances, les crises sanitaires et promouvoir et animer des campagnes de prévention sur le territoire local et national.

3 Manque de données épidémiologiques françaises

3.1 Les Intoxications et les CAP dans le monde

Les intoxications sont une cause importante de morbidité et de mortalité dans le monde et représentent une menace pour la santé publique [21–23], en particulier pour les enfants, selon un rapport de l'Organisation Mondiale de la Santé (OMS) [24–26]. Les expositions peuvent être de nature pharmaceutique, chimique, professionnelle ou environnementale.

Les progrès technologiques ont accéléré la vitesse à laquelle de nouveaux produits chimiques sont mis à la disposition du public, augmentant l'incidence d'effets indésirables. Notre capacité à détecter les produits exogènes dans l'organisme et l'environnement a également, considérablement augmenté au cours des deux dernières décennies.

Pour endiguer l'incidence croissante de l'exposition aux substances toxiques ainsi que la morbidité et mortalité associées, le siècle dernier a vu la création et l'évolution de centres antipoison dans le monde entier [27–31]. Selon les pays, les CAP varient en termes de modèle de dotation, de services offerts et de sources de financement.

De nombreuses études ont démontré la rentabilité des CAP en termes de nombre de visites aux services d'urgence évitées et de diminution de la durée de séjour à l'hôpital [32–36].

3.2 CAP dans le monde et études épidémiologiques

Cependant, il y a encore peu de données disponibles dans la littérature, sur des bases de données tels que PubMed, quant à l'épidémiologie des intoxications en France.

Les études descriptives épidémiologiques [26,37] nous permettent d'objectiver ou d'anticiper des crises de santé publique, et plus particulièrement dans le cadre de la toxicovigilance, des tendances d'intoxications ou de mauvais usage nocifs pour la population. Celles-ci peuvent nous permettre d'entreprendre, entre autres, la mise en

place de campagnes de prévention, de retrait de produits, de formations de médecins ou d'une éducation de la population.

Il existe plusieurs pays dans le monde où un rapport systématique centralisé est publié. L'association américaine des centres antipoison publie depuis de nombreuses années un rapport annuel systématique complet avec des tendances actuelles et des perspectives pour le futur [38]. Ce rapport est exhaustif et permet de faire le point annuellement sur des crises de santé publique comme la « Crise des opioïdes aux Etats Unis » [39,40].

En Europe, de multiples pays procèdent à une publication similaire comme la Suède, le Danemark, la Pologne, le Royaume-Uni ou l'Irlande [41–47]. Au Moyen-Orient on retrouve également des rapports similaires, surtout en Israël [48–54], basés sur le modèle américain. En Afrique, le nombre d'analyses épidémiologiques retrouvé sur PubMed, Elsevier Masson ou Google Scholar reste très limité [55,56].

Il existe très peu de données épidémiologiques publiées en France sur des bases de données de références médicales [57]. Le rapport de Toxicovigilance de l'ANSES n'est pas exhaustif et n'étaye que les tendances de l'année de sa publication [58,59]. Il est pourtant indispensable d'avoir des données épidémiologiques concrètes et comparables afin de promouvoir une meilleure prévention publique, ambulatoire et hospitalière.

Nous avons donc voulu réaliser une analyse descriptive de la base de données CIGUE du CAPTV de Lille entre 1988 et 2020 avec des critères transposables et comparables avec les études internationales.

4 Objectif

L'objectif stratégique de ce travail est de décrire certaines tendances de recours aux soins pour en déduire des pistes d'amélioration dans l'éducation sanitaire et la prévention en ambulatoire.

Afin de contribuer à cet objectif, l'objectif opérationnel de ce travail est d'analyser les données de la base de données centrale CIGUE du CAPTV de Lille entre 1988 et 2020.

Article en Anglais

1 Introduction

1.1 Poisoning around the world

Poisoning is an important cause for mortality and morbidity around the world and is a concern for public health authorities [21–23], specifically for children [24–26]. Exposures can be pharmaceutical, chemical, occupational or environmental. Advances in technology have accelerated the rate at which new chemicals, medical or non-medical, are made available to the public. This increases the incidence of adverse effects. But our ability to detect chemicals in the body and the environment has also increased dramatically over the past two decades.

To stem this growing incidence of exposure to toxic substances and the associated morbidity and mortality, the last century has seen the establishment and development of poison control centers around the world [27–31]. Depending on the country, poison centers vary in terms of endowment model, services offered and sources of funding.

Numerous studies have demonstrated the cost-effectiveness of poison centers in terms of the number of emergency department visits avoided and the reduction in the length of stay in the hospital [32–36].

1.2 Poison centers and epidemiological studies

Descriptive epidemiological studies [26,37] allow to objectify or anticipate public health crises, and more particularly in the context of toxicovigilance, poisoning trends or harmful misuse for the general population. These can allow to undertake, among other things, the establishment of prevention campaigns, product withdrawals, better training for doctors, and education of the general population.

There are several countries in the world where a centralized systematic report is published. For many years, in the US, the American Association of Poison Centers have been publishing annually a systematic report complete with current trends and prospects for the future [38]. This report is exhaustive and provides an annual update on public health crises such as the “Opioid crisis in the United States” [39,40].

In Europe, multiple countries make a similar publication such as Sweden, Denmark, Poland, United Kingdom or Ireland [41–47]. In the Middle East and Asia we also find similar reports, especially in Israel [48–54,60]. In African countries, the number of epidemiological studies found on PubMed, Elsevier Masson or Google Scholar remains very limited [55,56].

1.3 French toxicologic epidemiological data

Unfortunately, there are very few toxicologic epidemiological data published in France on databases of medical references [57,61]. The ANSES (French National agency of Food and Drug administration) toxicovigilance annual report is not exhaustive and only showcases the trends of the year of its publication [58,59].

However, it is essential to have concrete and comparable epidemiological data in order to promote better public, private and hospital prevention.

In Lille, in the North of France, every call to the Poison Center has been registered in the CIGUE database, since 1988.

1.4 Objectives

The strategic objective of this work is to describe trends related to primary care in order to inform general practitioners, and contribute to the prevention of outcomes for patients treated on an outpatient basis.

In order to contribute to this objective, the operational objective of this work is to analyze the data from the CIGUE database from 1988 to 2020 ("CIGUE analysis"). An exhaustive literature review will be first performed, in order to identify the indicators that should be computed ("literature review").

2 Material and methods

2.1 Literature review

An exhaustive review of literature of annual reports, reviews and epidemiological studies made in poison centers of countries around the world was made to determine which metrics and indicators were important, and which classifications and methodology should be implemented.

We used the keywords presented in (Table 1) to create a query.

Table 1. Lists of words used for the bibliographic query

Concept 1	Concept 2	Concept 3
anti poison center	nationwide	epidemiology
poison center	database	epidemiologic
poison control	poison(s)	descriptive
poison control center	information	incidence
npis	general	prevalence
national poison information service	emergency department	frequency
national poisons information service(s)	call(s)	trends
american association of poison control centers	telephone	insights
centre anti poison	big data	risk(s)
toxico vigilance	data	epidemiological
national poison data system	hospital admission	insight
poison centre	serious medical outcomes	trend
poison information centre(s)	phone calls	public health
base nationale des cas d'intoxication	report(s)	
BNCI	review(s)	
poisoning(s)	hotline	
	service(s)	
	status	

This query was used on http://pubmed.gov. The same keywords were used on http://sciencedirect.com and http://scholar.google.com.

For instance, on Pubmed.gov, we used the following query:

```
(("anti poison center"[Title/Abstract]) OR ("poison
center"[Title/Abstract]) OR ("poison control"[Title/Abstract]) OR ("poison
control center"[Title/Abstract]) OR ("npis"[Title/Abstract]) OR ("national
poison information service"[Title/Abstract]) OR ("national poisons
information service"[Title/Abstract]) OR ("national poisons information
services"[Title/Abstract]) OR ("american association of poison control
centers"[Title/Abstract]) OR ("centre anti poison"[Title/Abstract]) OR
("toxico vigilance"[Title/Abstract]) OR ("toxico-
vigilance"[Title/Abstract]) OR ("national poison data
system"[Title/Abstract]) OR ("poison centre"[Title/Abstract]) OR ("poison
information centre"[Title/Abstract]) OR ("poison information
centers"[Title/Abstract]) OR ("Base nationale des cas
d'intoxication"[Title/Abstract]) OR ("BNCI"[Title/Abstract]) OR
("poisonings"[Title/Abstract]) OR ("poisoning"[Title/Abstract]) ) AND
(("nationwide"[Title/Abstract]) OR ("database"[Title/Abstract]) OR
("poison"[Title/Abstract]) OR ("information"[Title/Abstract]) OR
("general"[Title/Abstract]) OR ("emergency department"[Title/Abstract]) OR
("call"[Title/Abstract]) OR ("telephone"[Title/Abstract]) OR ("big
data"[Title/Abstract]) OR ("data"[Title/Abstract]) OR ("hospital
admission"[Title/Abstract]) OR ("serious medical outcomes"[Title/Abstract])
OR ("phone calls"[Title/Abstract]) OR ("report"[Title/Abstract]) OR
("reports"[Title/Abstract]) OR ("calls"[Title/Abstract]) OR
("hotline"[Title/Abstract]) OR ("service"[Title/Abstract]) OR
("services"[Title/Abstract]) OR ("status"[Title/Abstract]) OR
("review"[Title/Abstract]) OR ("reviews"[Title/Abstract]) ) AND
(("epidemiology"[Title/Abstract]) OR ("epidemiologic"[Title/Abstract]) OR
("descriptive"[Title/Abstract]) OR ("incidence"[Title/Abstract]) OR
("prevalence"[Title/Abstract]) OR ("frequency"[Title/Abstract]) OR
("trends"[Title/Abstract]) OR ("insights"[Title/Abstract]) OR
("risk"[Title/Abstract]) OR ("epidemiological"[Title/Abstract]) OR
("insight"[Title/Abstract]) OR ("risks"[Title/Abstract]) OR
("trend"[Title/Abstract]) OR ("public health"[Title/Abstract]) )
```

Only scientific papers and reports issued from poison centers were considered. The documents were filtered by reading the title, and then the abstract, and then the full text. The full text was retrieved using web search engines, and by contacting the authors by email.

From the selected papers, we extracted the various indicators reported by the authors and, when available, the way the indicators were computed.

2.2 CIGUE analysis

2.2.1 Database

The CIGUE database which began collecting data in 1995 is the data repository for all calls and cases registered at the Lille CAPTV and includes all case information collected by its predecessor ARSENIC from 1988 until 1999. These two databases were merged in 1999 under the name CIGUE. The last call registered on CIGUE was on 2020. The database is still used for protocol inquiry but no longer for case collecting. This database is made of 53 tables all fulfilled by the medical doctors (or residents and/or assistants) and clinical pharmacists of the CAPTV of Lille.

This study focuses on exposure cases, as a single call can generate multiple cases. All substance cases were singled out, as a single call can be for multiple substances. This analysis excluded records corresponding to simple information requests, without

explicit exposure. Only human exposures were analyzed. We included non-duplicate cases that were classified as CLOSED by medical staff. A case is considered closed when it is determined that no further follow-up or recommendation is needed, or when no additional information is available. Exposure cases are meticulously tracked to ensure the most accurate medical outcomes. Most cases are closed within a few hours of the initial contact, though cases involving complex hospitalized patients or fatalities may remain open for months to allow ongoing data collection. Follow-up contacts are crucial for monitoring the appropriateness of management recommendations, continuously updating case information, enhancing patient guidelines, providing poison prevention education, and obtaining final medical outcomes to ensure the accuracy and completeness of the collected data.

An extraction was performed using SQL queries.

2.2.2 Data analysis

We computed the indicators identified from the literature review.

2.2.3 Statistical analysis

Qualitative, binary, or discrete variables with very few modalities are expressed in numbers and percentages.

Quantitative variables are expressed as mean and standard deviation (SD) if the histogram reveals a symmetrical pattern distribution, and median first and third quartile (Q1, Q3) otherwise.

The independence between two qualitative variables is tested using a Chi-square test.

Statistical tests are bilateral. The *p* values are considered significant at the 5% threshold. P values under 10^{-10} are reported as “p=0”.

2.2.4 Regulatory framework

This study was made under the regulatory status of MR004 of the French national agency for data privacy, the CNIL [62].

3 Results

3.1 Literature review

After screening 10,361 studies on PubMed and 26 studies on Google Scholar and Elsevier Masson, we finally included 17 studies (Figure 2).

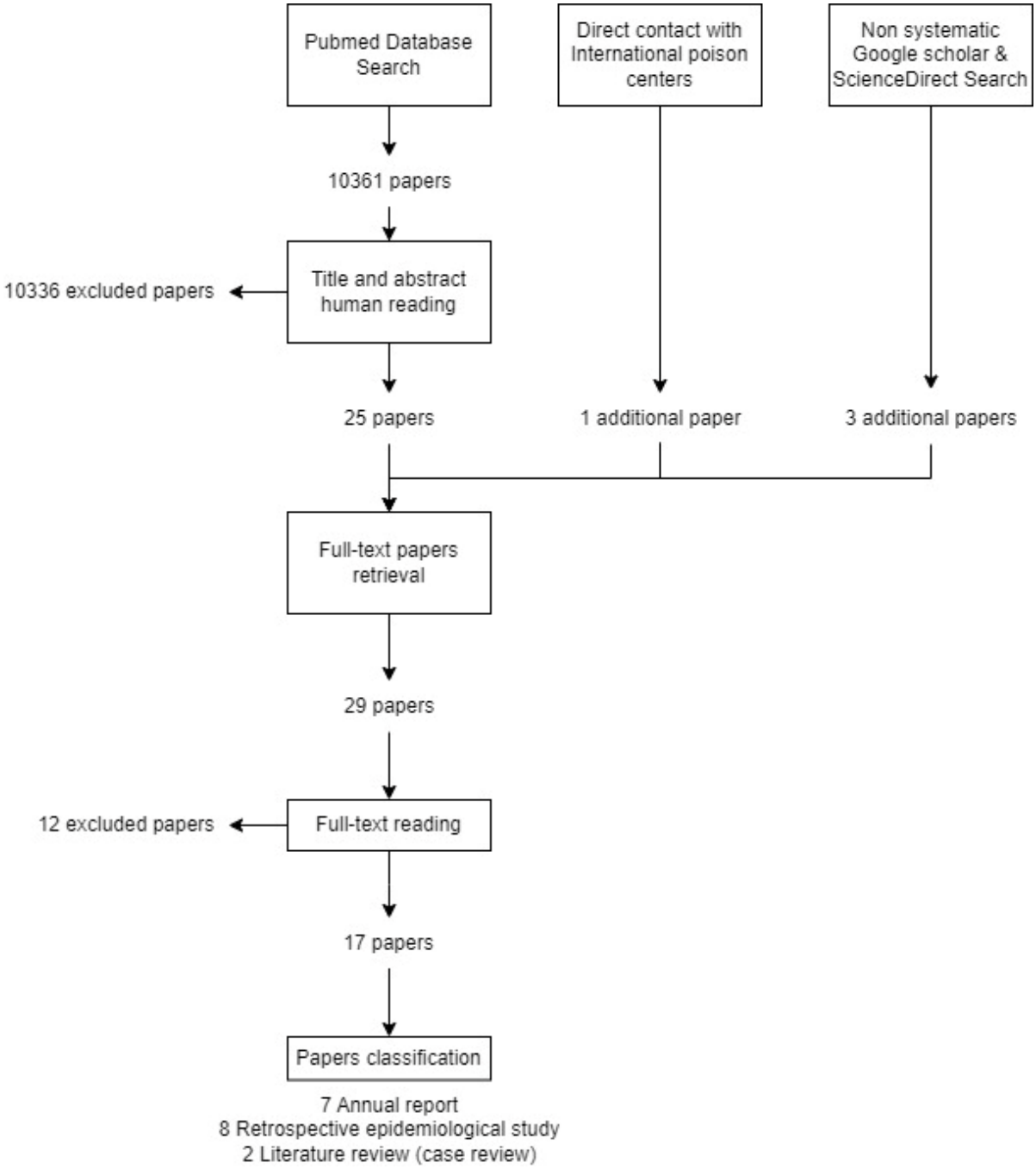


Figure 2. Flowchart of the literature review

The key elements that were common to almost all studies were the characterization of the incoming calls, the exposed population, the reasons, the substances used, the characterization of fatality cases, the trends and evolutions in time. Most of the studies also detailed the use of certain types of substances, especially pharmaceutical products. The complete list of indicators is presented in (Table 2).

Table 2. Key indicators of the AAPC's Annual Report (first reference) and international studies (next references)

Indicators \ Studies	AAPC Annual Report [38]	Iran [60]	Pakistan [49]	Poland [43]	East Africa [55]	Turkey [50]	Ethiopia [56]	Israel [48]	Ireland [45]	Lille 2006 [9]	Marseille 2002-2012 [57]	Suisse [47]	Hong Kong [53]	India [54]	Denmark [42]	Sweden [41]	Taiwan [51]
Number of exposures	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Seasonal distribution	x					x			x	x	x					x	
Type/mode of exposures	x				x	x	x	x	x				x				x
Information request type	x								x	x	x			x			
Fatality case review	x		x							x		x					x
Age/Gender distribution	x	x	x	x	x	x		x	x	x	x	x	x	x		x	x
Number of substances involved	x																
Site of call/exposure	x	x	x		x	x		x	x	x	x		x	x			
Population-adjusted exposures	x																
Reasons	x	x		x	x	x			x	x	x	x	x	x		x	x
Scenarios, by age	x																
Distribution of reason for exposure by age	x	x				x											x
distribution of reason for exposure and age for fatalities	x																
Route of exposure	x					x	x	x		x			x	x			x
Management site	x					x		x									
Clinical outcome	x		x				x	x	x	x		x	x				x
medical outcome of human exposure cases by patient age	x							x									
medical outcome by reason for exposure	x							x									x
duration of clinical effects by medical outcome	x					x											
Decontamination and therapeutic interventions	x					x		x					x				
Therapy provided by age	x																
Decontamination and antidote trends	x					x							x				
Most frequent substances categories in human exposure cases	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
rate over years	x		x	x		x					x		x		x		
most frequently involved in pediatric exposure	x			x		x		x	x		x			x		x	x
most frequently involved in pediatric deaths	x					x		x									x
most frequently involved in adult exposures	x		x	x				x	x		x		x	x		x	x
most frequently identified in drug identifications	x								x								x
most frequently involved in pregnant exposures	x																
categories associated with largest number of fatalities	x																x
Comparisons of death data	x				x												

3.2 CIGUE analysis

3.2.1 Description of the calls

3.2.1.1 Distribution over time

The total number of calls analyzed was 662,140. They were mostly concentrated between 8:00 and 00:00 with peaks between 11:00 and 13:00, and 18:00 and 22:00 (Figure 3).

The number of calls the CAP of Lille has received, between 1992 and its peak in 2013, has almost tripled, from 9,923 in 1992 to 28,128 cases a year in 2013 (Figure 5). After this date the calls dwindle till the last one in 2020.

Calls are distributed rather evenly throughout the week with Wednesday (Figure 4) being the busiest day with 98,962 calls (14.9%). In monthly distribution, the period between May and June seems to be busier than usual: we observed 60,370 calls in June (9.1%) and 59,246 calls in May (8.5%).

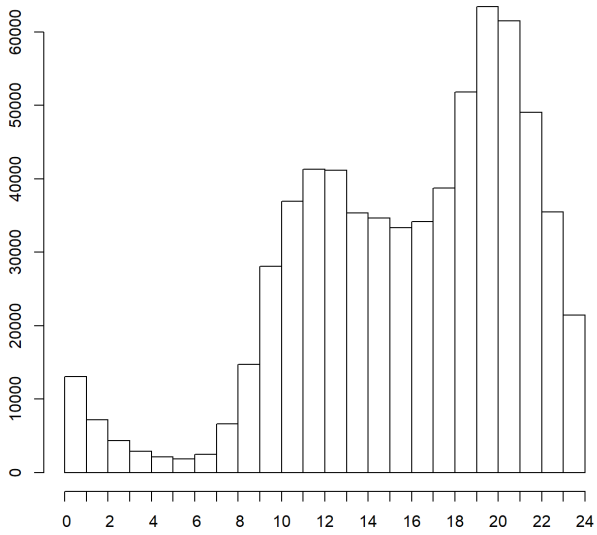


Figure 3. Hourly distribution of calls

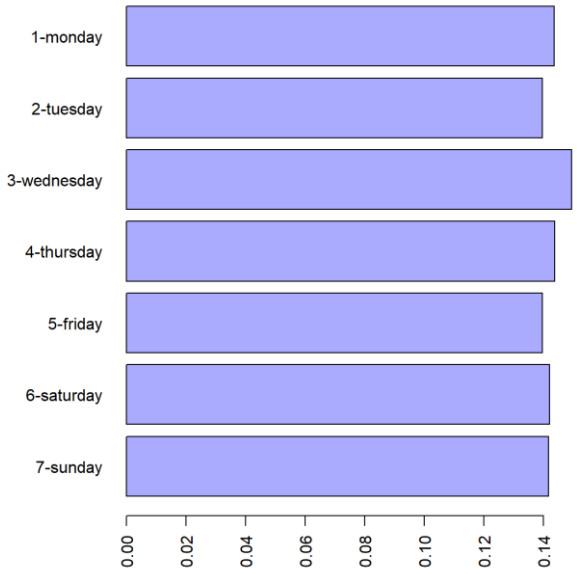


Figure 4. Weekly distribution of calls

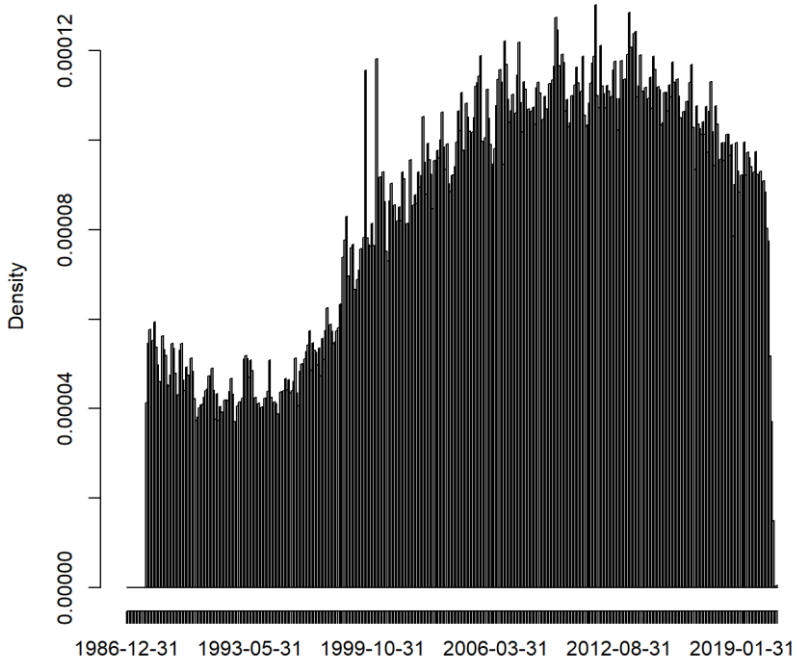


Figure 5. Density of calls over the years (p=0 for counts comparison over years)

3.2.1.2 Description of the calls

3.2.1.2.1 The caller

The total number of calls analyzed was 651,085. The most frequent caller was the family of the patient with 244,159 (36.5%) calls, followed by hospital staff (medical or paramedical) with 172,139 (26.4%); the SAMU (French medical emergency dispatch service) with 94,103 (14.5%); the patient himself with 53,060 (8.2%); non hospital paramedic staff with 35,982 (5.5%); general practitioner with 32,255 (5%) (Table 3, Figure 6).

Table 3. Caller distribution

Caller	N	Proportion
Family/Friend	244159	37.5%
Hospital staff	172139	26.4%
SAMU	94103	14.5%
Patient	53060	8.2%
Non hospital paramedical staff	35982	5.5%
General practitioner	32255	5%
General public	5403	0.8%
Social institutions	5325	0.8%
Paper archive	5087	0.8%
Other non-hospital doctors	2714	0.4%
Public services	740	0.1%
Prison	60	0.01%
Unknown	58	0.01%
TOTAL	651085	100%

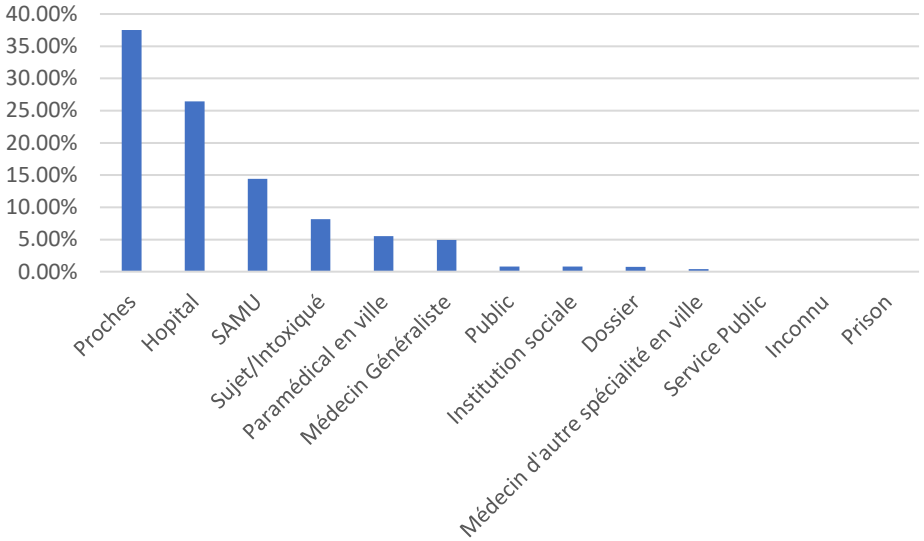


Figure 6. Caller Distribution

3.2.1.2.2 The location of the caller

We observe, over 662,179 cases, most of the calls come from the French department of the *Nord* (59) with 215,470 (32.5%) calls, followed by the region of *Ile-de-France* with 118,161 (17.8%) calls, other regions with 94,450 (15.8%) calls, *Normandie* with 94,450 (14.3%) calls, *Pas-de-Calais* (62) with 78,767 (11.3%) calls, and other departments of *Hauts-de-France* with 50,588 (11.3%) calls (Figure 7).

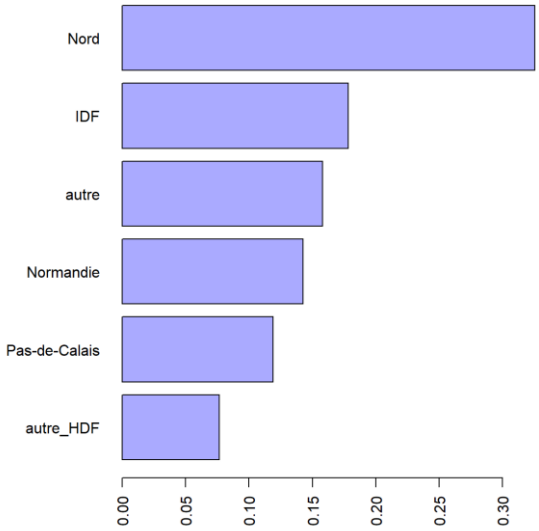


Figure 7. Geographical origin of the calls
(IDF: Ile de France, autre_HDF: other departments of Hauts de France, autre=other departments)

3.2.1.2.3 Exposure site

We observe that over 662,179 calls, most of the human exposure cases happened at the residence (own or other) of the patient with 592,167 (89.4%) calls, followed with the workplace with 20,044 (3.0%) calls, health care facility with 19,986 (3.0%) calls, school or educational establishment with 12,104 (1.8%) calls (Table 4).

Table 4. Site of call for human exposure cases

Site of call	N	Proportion
Residence	592,167	89.4%
Workplace	20,044	3.0%
Health care facility	19,986	3.0%
School	12,104	1.8%
Outdoors	9,357	1.4%
Other	5,778	0.9%
Public area	2,489	0.4%
Agricultural area	254	0.04%
TOTAL	662,179	100%

3.2.1.3 Description of the patient

Among all the calls, 641,590 had their age described. The calls were mostly for children between the ages of 1 and 5 with 298,712 cases (46.6%; Table 5, Figure 8).

Table 5. Age Group distribution of the calls

Age group	N	Proportion
[0,1)	32,729	5.1%
[1,2)	109,143	17.0%
[2,3)	106,883	16.7%
[3,5)	82,686	12.9%
[5,13)	54,542	8.5%
[13,20)	53,504	8.3%
[20,30)	48,587	7.6%
[30,40)	48,312	7.5%
[40,50)	37,655	5.9%
[50,60)	27,003	4.2%
[60,70)	16,843	2.6%
[70,80)	11,086	1.7%
[80,90)	9,311	1.5%
[90,150)	3,306	0.5%
TOTAL	641,590	100%

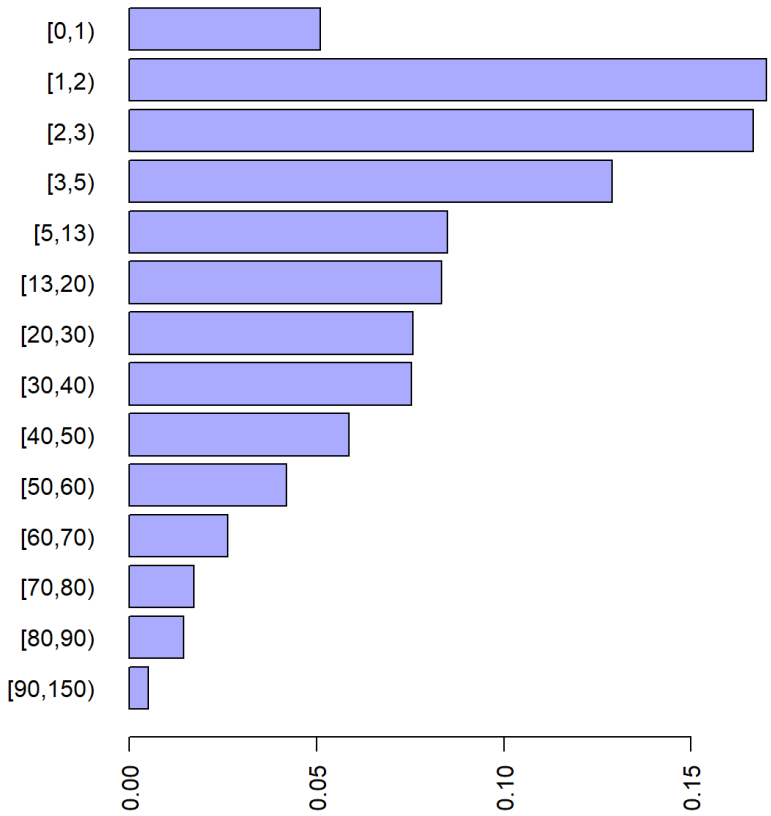


Figure 8 Distribution of calls by age group of the patient

Among all the patients, 335,503 (51.2%) were female; 4,279 (1.3% of them) were pregnant.

3.2.2 Reason of exposure

Among all the calls, 662,179 calls had the type of exposure described. Most of the calls were categorized as domestic accident with 449,857 (67.9%), followed by suicidal behavior with 83,965 (12.7%), therapeutic accident with 81,339 (12.3%),

Work or school related with 18,470 (2.8%), voluntary intoxication (excluding suicidal behavior) 15,890 (2.4%), linked to the environment 6,866 (1.0%), criminal or incendiary related 5,393 (0.81%), other 399 (0.1%) (Table 6).

Table 6. Reason for human exposure cases

Type	N	Proportion
Involuntary		
➢ Domestic accident	449,857	67.9%
➢ Therapeutic Accident	81,339	12.3%
➢ Work/School Related	18,470	2.8%
Voluntary		
➢ Suicidal Behavior	83,965	12.7%
➢ Voluntary Intoxication (Misuse/Abuse/Unknown)	15,890	2.4%
Environmentally linked	6,866	1.0%
Criminal/Incendiary related	5,383	0.8%
Other	399	0.1%
TOTAL	662,179	100%

3.2.2.1 Domestic accidents

Among 662,179 calls, 449,857 (67.9%) were categorized as domestic accidents.

The number of domestic accidents grew consistently from 8,080 cases in 1988 to 13,994 in 2019, with a peak of 19,189 cases in 2009 (Figure 9)

The percentage of calls linked to domestic accident over the years remained stable, ranging from 63.0% in 1988 to 66.8% in 2014 (p=0, Figure 10).

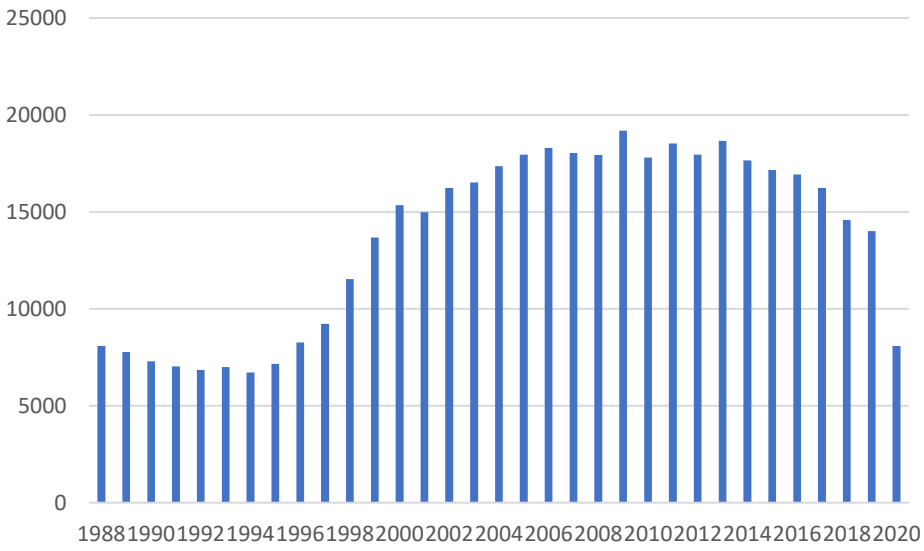


Figure 9. Domestic accidents over the years

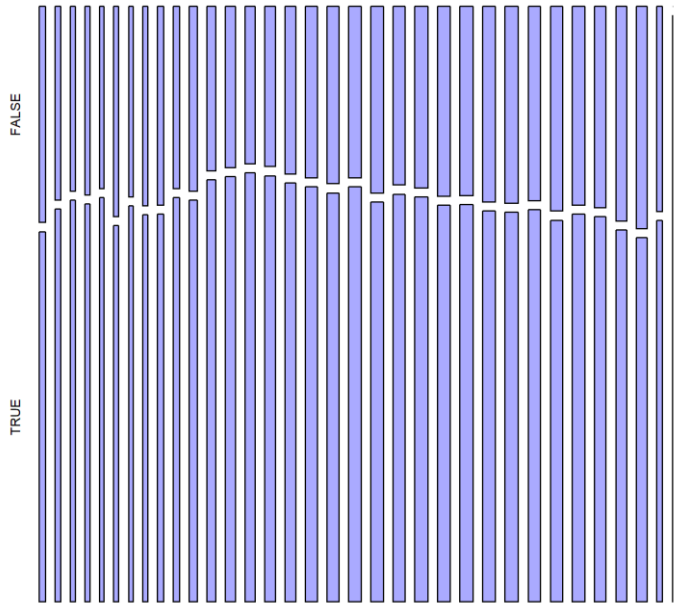


Figure 10. Proportion of domestic accidents, as a function of the year (from 1988 to 2020; p=0)

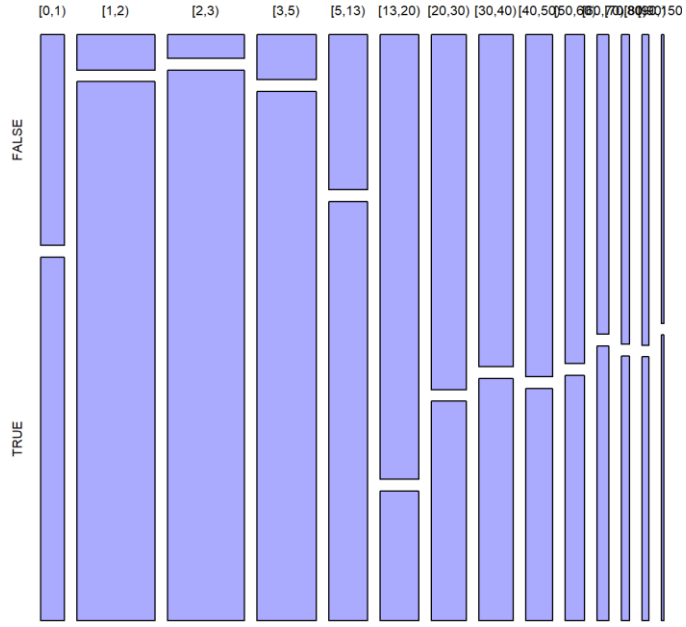


Figure 11. Proportion of domestic accidents, by age class (p=0)

The calls mostly related to children between 0 and 13 years old. The proportion of domestic accidents depended on the age class: this proportion represented 63.2% of calls for the 0-1 age class; 93.8% of calls for the 1-2; 95.8% for the 2-3; 92.1% for the 3-5; 73% for the 5-13; 22.6% for the 13-20; 38.1% for the 20-30; 42.1% for the 30-40; 40.4% for the 40-50; 42.7% for the 50-60; 47.8% for the 60-70; 46.0% for the 70-80; 45.9% for the 80-90; 49.7% for 90 and more (p=0, Figure 11).

3.2.2.2 Suicidal Behavior

Among 662,179 calls, 83,965 (12.7%) were categorized as suicidal behavior. The number of calls categorized as suicidal behavior grew over the years from 1,861 cases in 1992 to 2,548 in 2019, with a peak of 3048 cases in 2013 (Figure 12).

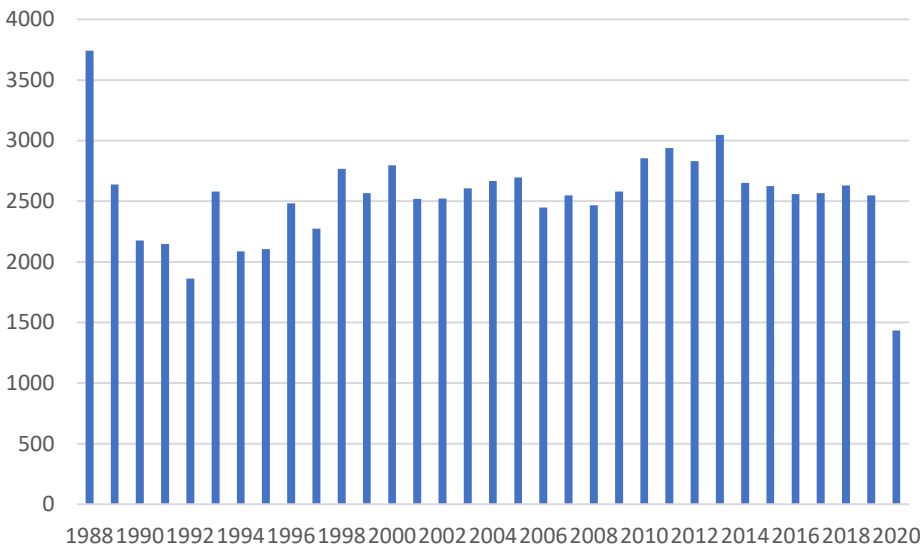


Figure 12. Suicidal behavior over the years

The proportion of suicidal behavior depended on the age class: this proportion represented 56.0% of calls for the 13-20 age class, 30.7% for the 20-30; 27.2% for the 30-40; 28.0% for the 40-50; 21.9% for the 50-60; 13.8% for the 60-70; and 9.2% for the 70-80 (p=0, Figure 13).

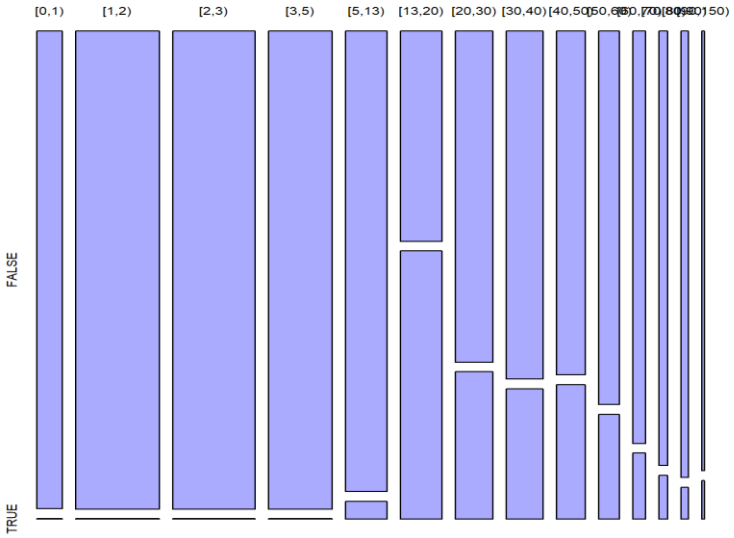


Figure 13. Proportion of suicidal behavior, by age class (p=0)

3.2.2.3 Therapeutic error or accident

Among 662,179 calls, 81,339 (12.3%) were categorized as therapeutic errors or accidents.

The number of cases a year grew over the years from 625 cases in 1988 to 4,251 in 2019 (Figure 14)

The proportion of therapeutic accidents also grew consistently over the years from 4.88% in 1988 to 18.84% in 2019 (p=0, Figure 15).

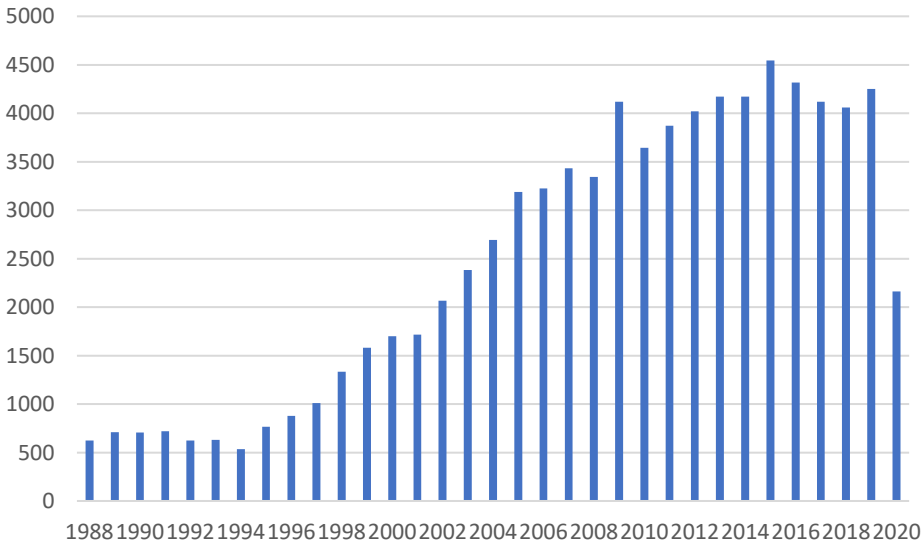


Figure 14. Therapeutic accidents over the years

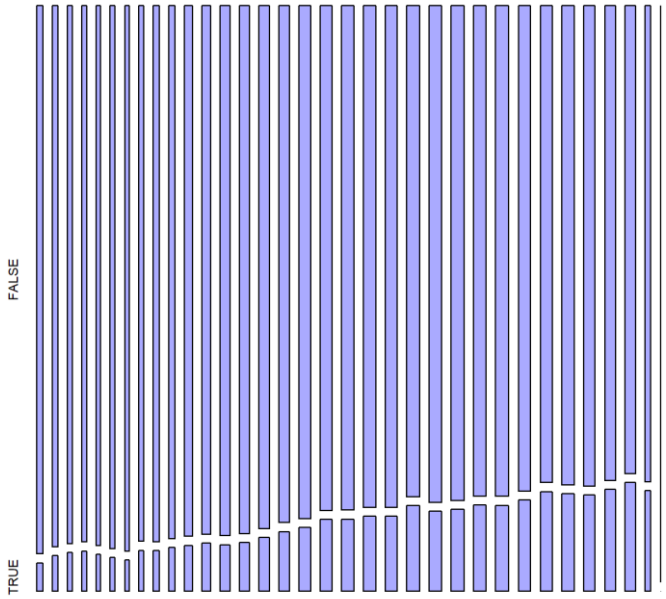


Figure 15. Proportion of therapeutic accidents over the years (p=0)

The calls related to therapeutic errors mostly concern children between 0 and 1 year old and between 5 and 13 years old. Among adults, the risk of therapeutic error increased with the age.

The proportion of therapeutic errors or accidents depended on the age class: this proportion represented 34.6% of calls for the 0-1 age class; 5.7% of calls for the 1-2; 3.8% for the 2-3; 6.9% for the 3-5; 17.0% for the 5-13; 8.8% for the 13-20; 11.4% for the 20-30; 13.3% for the 30-40; 15.9% for the 40-50; 22.9% for the 50-60; 31.3% for the 60-70; 37.8% for the 70-80; 37.7% for the 80-90; 30.9% for 90 and more (p=0, Figure 16).

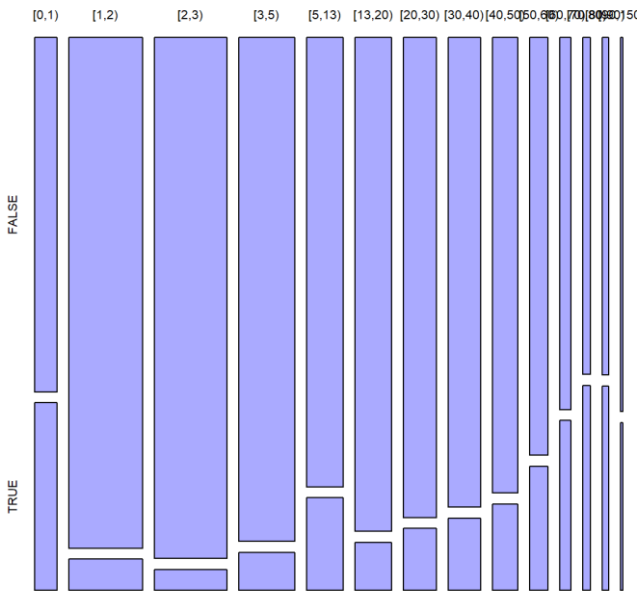


Figure 16. Proportion of therapeutic accidents by age group (p=0)

3.2.3 Clinical severity on call

The clinical severity was described over 662,179 calls. We observed a severity on call described as asymptomatic for 364,126 (55.0%) calls, low to moderate for 201,860 (30.5%) and severe to lethal for 4,696 (0.7%). For 91,497 (13.8%) cases, the severity was described as unknown or other. Among non-missing values, we observed a stable proportion of severity on call over the years (p=0, Figure 17, Table 8) after 1993.

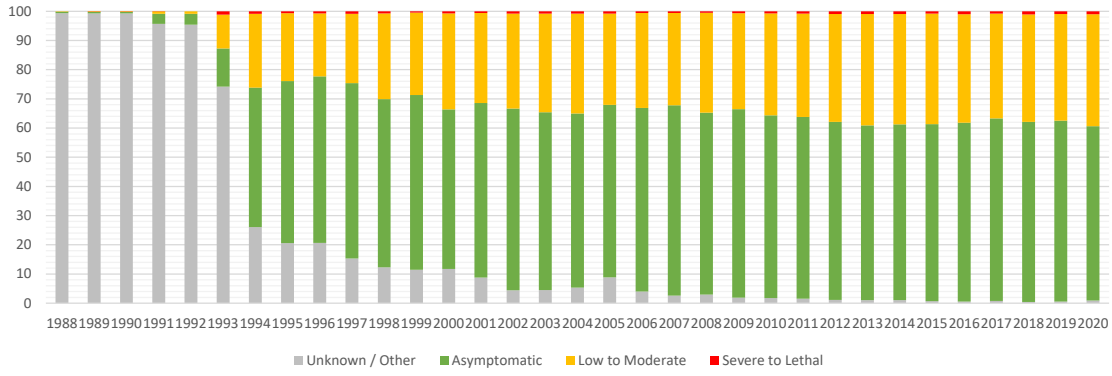


Figure 17. Proportion of severity on call over the years (p=0)

The severity on call varies with the reason of the call (Figure 18, Table 9). 2,954 cases of suicidal behavior had severe to lethal symptoms (3.5% of the proportion of suicidal behavior, p=0).

Most of domestic accidents had a severity on call described as asymptomatic with 268,926 cases (59.8% of the proportion of domestic accidents, p=0). or low to moderate with 121,410 cases (27,0% of the proportion of domestic accidents, p=0).

Therapeutic accidents also had a severity on call described as asymptomatic with 57,361 cases (70.5% of the proportion of therapeutic accidents, p=0) or low to moderate 18,001 cases (22.1% of the proportion of therapeutic accidents, p=0).

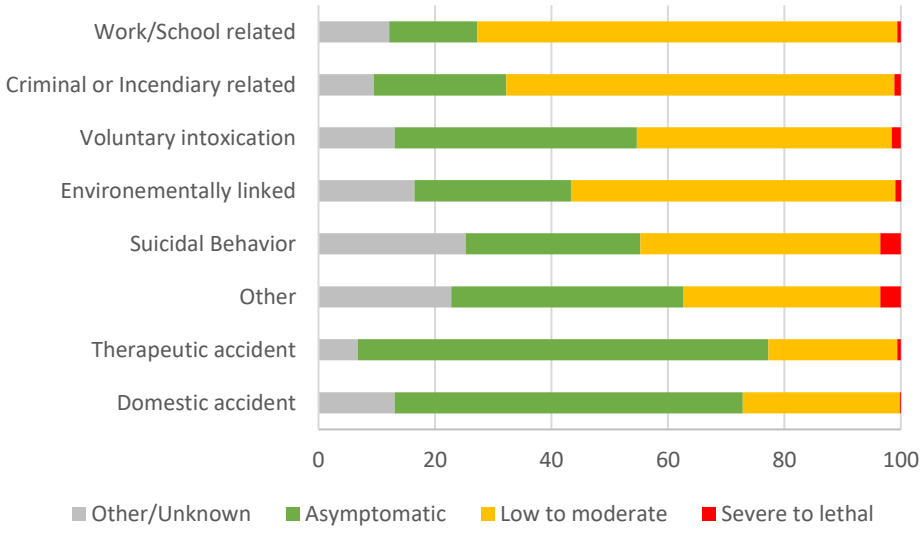


Figure 18. Proportion of severity on call by reason (p=0)

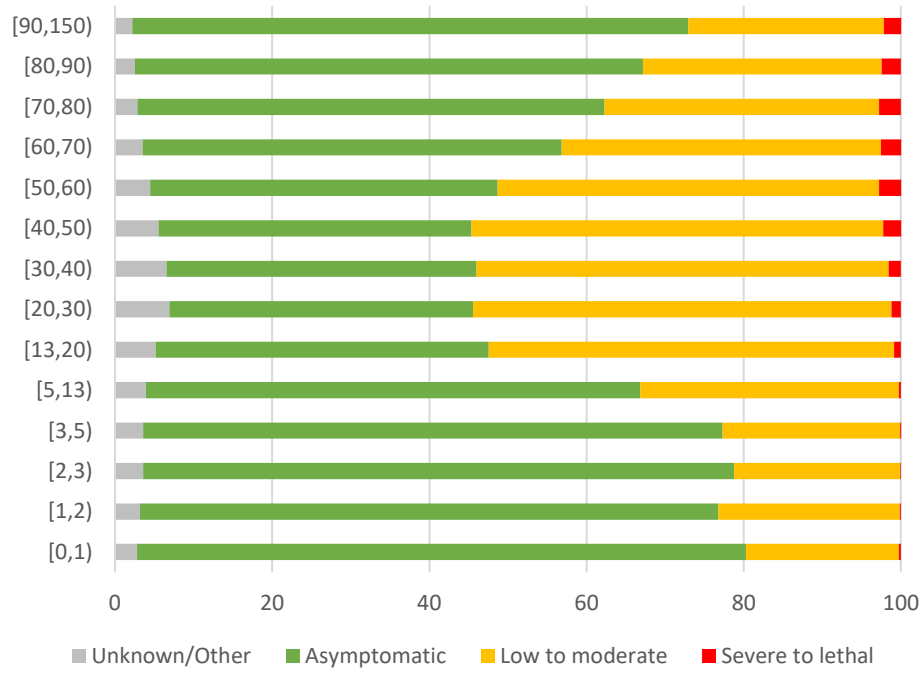


Figure 19. Proportion of severity on call by age class (p=0)

The proportion of a symptomatology categorized as severe to lethal depended on the age class: this proportion represented 0.2% of calls for the 0-1 age class; 0.1% of calls for the 1-2; 0.08% for the 2-3; 0.09% for the 3-5; 0.3% for the 5-13; 0.8% for the 13-20; 1.2% for the 20-30; 1.6% for the 30-40; 2.3% for the 40-50; 2.8% for the 50-60; 2.5% for the 60-70; 2.8% for the 70-80; 2.5% for the 80-90; 2.2% for 90 and more (p=0, Figure 19).

3.2.4 Clinical outcome

The number of calls analyzed was 662,133. Most of the calls were closed on follow ups as no effect. Only 574 cases were reported as lethal on follow ups. 151,624

cases (23.2%) were classified as unknown, lost to sight, wrong coordinates or refusal of hospitalization (Table 7).

Table 7. Clinical outcome on follow ups

Clinical outcome	N	Proportion
No effect	497,819	76.2%
Unknown	151,624	23.2%
Complications / Sequelae	3,315	0.5%
Lethal	574	0.1%
TOTAL	662,133	100%

3.2.5 Analysis by substances

Among 662,179 cases, the substances most frequent in human exposures were household detergents with 163,177 (9.1%) cases, food (spoiled or not) with 323,752 (8.4%), benzodiazepine 93,945 (7.3%), paracetamol with 50,095 (5.7%) and solvents with 19,599 (5.5%) (Figure 20).

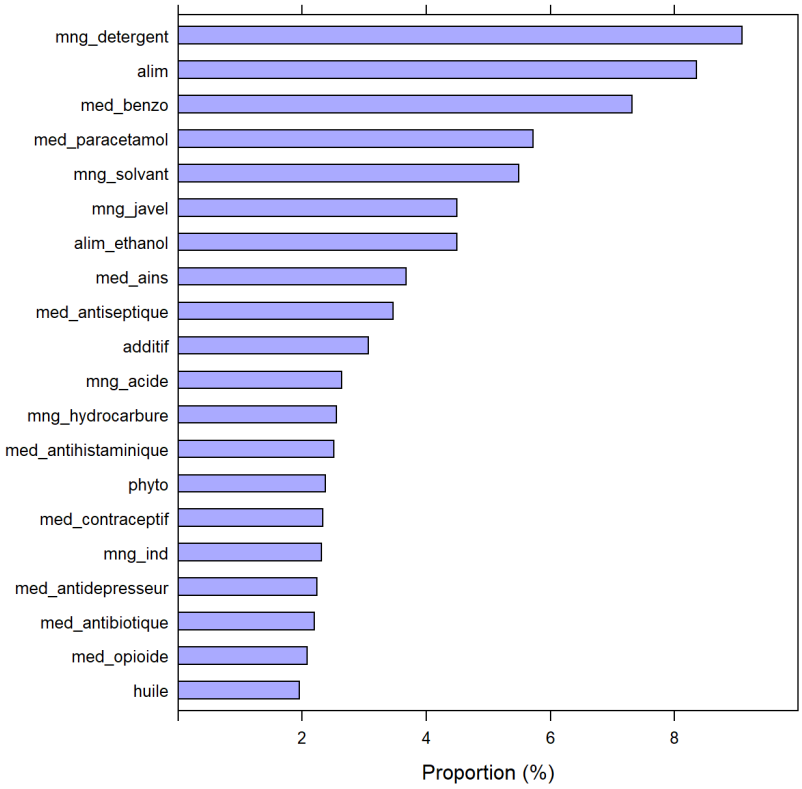


Figure 20. Proportion of substances in human exposures (p=0)

3.2.5.1 Household detergents

3.2.5.1.1 Number of cases

The number of cases grew over the years with 810 cases in 1988 to a peak in 2013 with 3,432 cases a year. Since then, we observe a decrease in number of cases a year with 2,103 cases in 2019 (Figure 21).

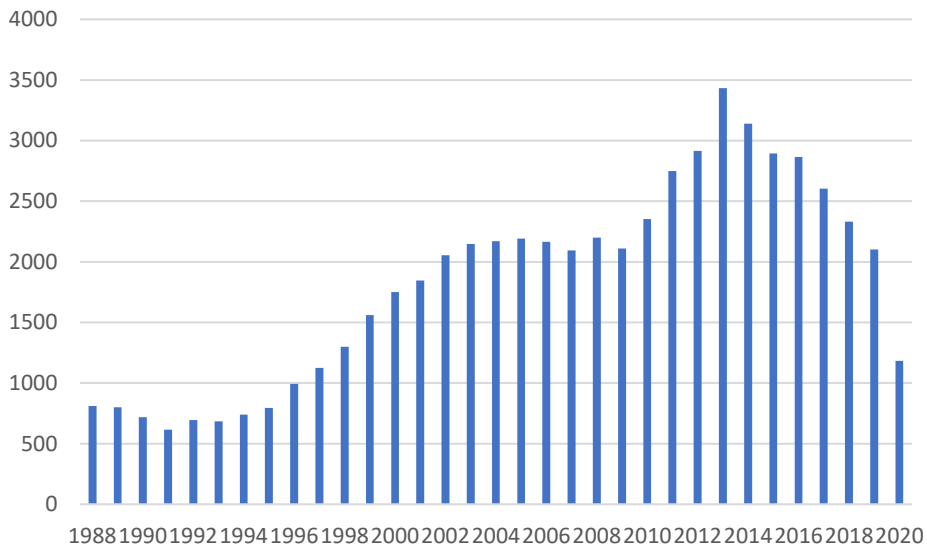


Figure 21. Household detergents exposure cases over the years

3.2.5.1.2 The age of the patients

Among 58,863 cases, the most exposed age group was the 1 to 2 years old with 19,909 cases (33.8%); followed by the age class 2-3 with 11,991 (20.4%); 3-5 age class with 6,861 (11.7%); 5-13 age class with 3,221 cases (5.5%).

3.2.5.1.3 Reasons for household detergent exposure

Among 60,142 cases, the most frequent reason for household detergent exposure cases is domestic accidents with 55,231 cases (91.8%); followed by suicidal behavior with 2,077 (3.5%), and work or school related with 1,436 cases (2.4%).

3.2.5.1.4 The severity on call for household detergent exposure

Among 60,142 cases, only 156 cases had their symptomatology categorized as severe to lethal. Most of the cases were categorized as asymptomatic (n=29,573) or low to moderate (n=24,245).

3.2.5.2 Benzodiazepines

3.2.5.2.1 Number of cases

The number of cases steadily grew from 1,304 cases in 1989 to a peak of 1,822 cases a year in 2010. Since then, the number of cases decreased with 1,103 cases in 2019 (Figure 22). In 2013, alprazolam with 343 cases became the most frequent cause of call for anxiolytic benzodiazepine followed by zolpidem with 284 cases and bromazepam with 271 cases per year.

There is a downward trend since 2013. In 2019, the number of cases per year for alprazolam was 255 (in 2010: N= 262), while zolpidem cases fell to 150 (in 2010, N=257) and bromazepam to 126 (in 2010, N= 348) (Table 10).

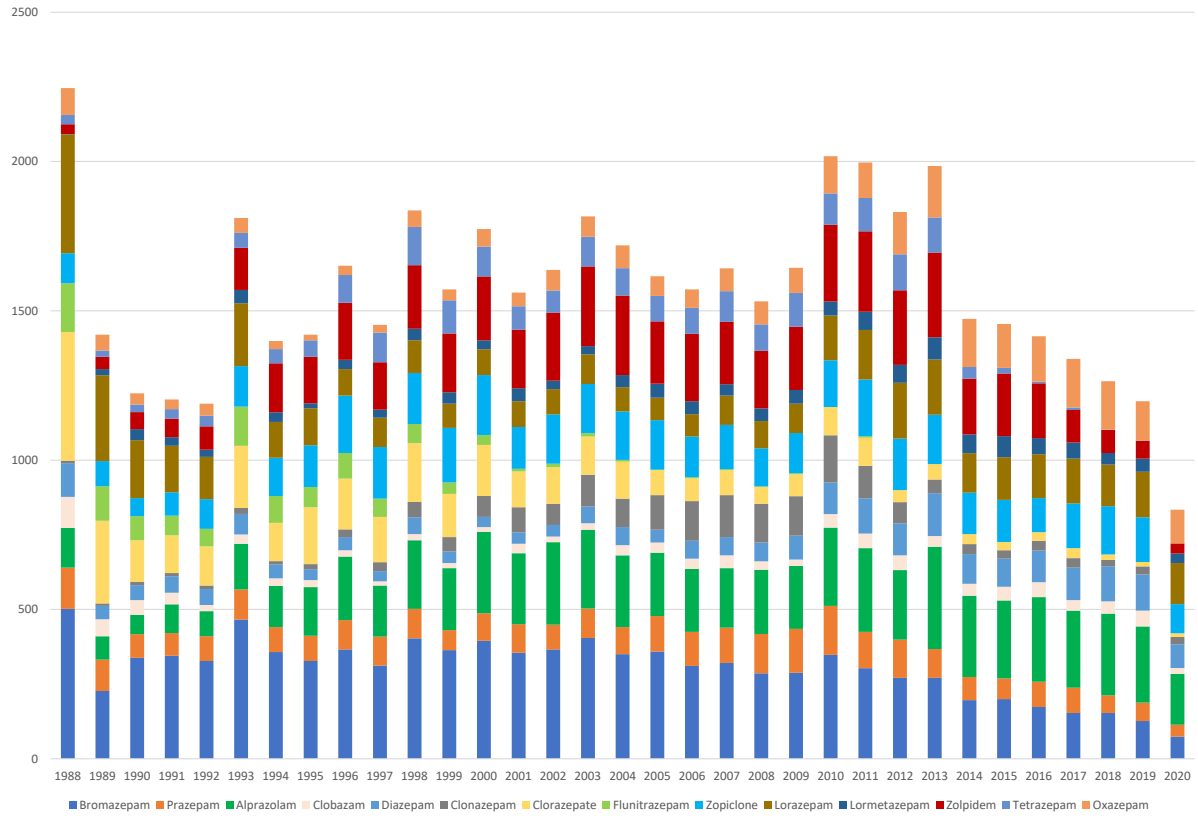


Figure 22. Different benzodiazepines exposures over the years

3.2.5.2.2 The age of the patients

Among 48,431 cases, the most exposed age group was the 13-20 years old with 8,986 cases (18.6%); followed by the age class 30-40 with 7,589 (15.7%); 20-30 age class with 7,173 (14.8%); 40-50 age class with 6,337 cases (13.1%).

3.2.5.2.3 Reasons for benzodiazepine exposure

Among 48,431 cases, the most frequent reason for benzodiazepine exposure cases was suicidal behavior with 30,842 cases (63.7%); followed by domestic accidents with 9,795 (20.2%), and voluntary intoxication (misuse/abuse/unknown) with 2,946 cases (6.1%).

3.2.5.2.4 The severity on call for benzodiazepine exposure

Among 48,431 cases, 1,143 (2.4%) cases had their symptomatology categorized as severe to lethal. Most of the cases were categorized as low to moderate (n=20,069) or asymptomatic (n=14,864).

3.2.5.3 Paracetamol

3.2.5.3.1 Number of cases

The number of cases steadily increased over the years with 406 cases in 1988 to 1,913 cases a year in 2019 with a peak in 2016 with 2,004 cases a year (Figure 23).

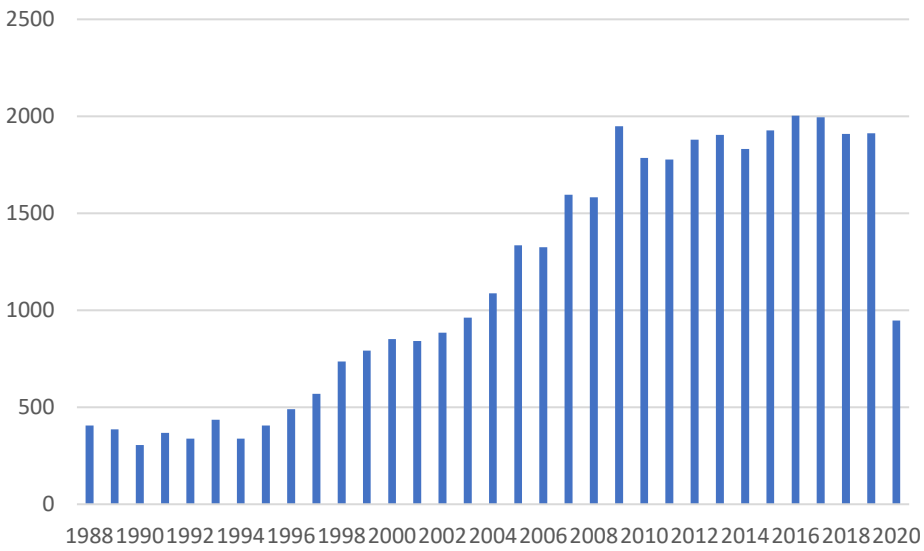


Figure 23. Paracetamol exposure cases over the years

3.2.5.3.2 The age of the patients

Among 37,879 cases, the most exposed age group was the 13-20 years old with 9,987 cases (26.4%); followed by the age class 2-3 with 5,640 (14.9%); 3-5 age class with 5,596 (14.8%); 20-30 age class with 3,115 cases (8.2%).

3.2.5.3.3 Reasons for paracetamol exposure

Among 37,873 cases, the most frequent reason for paracetamol exposure cases was domestic accident with 14,036 cases (37.1%); followed by suicidal behavior with 13,390 (35.4%), and therapeutic accidents/errors with 9,444 cases (24.9%).

3.2.5.3.4 The severity on call for paracetamol exposure

Among 37,873 cases, only 399 cases had their symptomatology categorized as severe to lethal. Most of the cases were categorized as asymptomatic (n=24,527) or low to moderate (n=9,566).

3.2.5.4 Opioids

3.2.5.4.1 Number of cases

The number of cases steadily grew over the years with 168 cases in 1988 to a peak in 2017 with 654 cases a year (Figure 24), representing a 389% increase for that period (1988-2017).

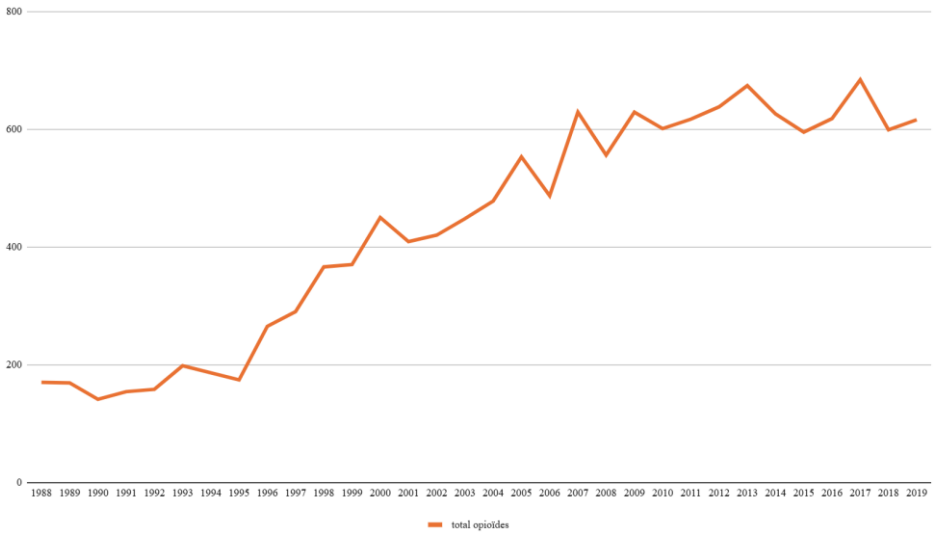


Figure 24. Opioid exposure cases over the years

3.2.5.4.2 The age of the patients

Among 13,487 cases, the most exposed age group was the 13-20 years old with 4,195 cases (31.1%); followed by the age class 20-30 with 1,776 cases (13.2%).

3.2.5.4.3 Reasons for opioid exposure

Among 13,792 cases, the most frequent reason of opioid exposure was suicidal behavior with 6,704 cases (48.6%); followed by therapeutic accidents with 3,407 (24.7%), domestic accidents 2,849 (20.7%), and voluntary intoxication with 761 cases (5.5%).

3.2.5.4.4 The severity on call for opioid exposure

Among 13,792 cases, only 387 cases had their symptomatology categorized as severe to lethal. Most of the cases were categorized as low to moderate (n=6,028) or asymptomatic (n=5,917).

3.2.5.4.5 Evolution over the years

We have observed a consistent increase in calls related to the use of codeine, tramadol, and opium from 1988 to 2020. Conversely, calls concerning dextropropoxyphene decreased from 2007 to 2015 (Table 11, Figure 25). From 1988 to 2017, tramadol exposure cases increased by 311%; codeine exposure cases by 229%; opium exposure cases by 730%. From 1988 to 2017, total mild opioid (Tramadol, Codeine, Opium) cases increased by 556%, while strong opioids (morphine) increased only by 187%.

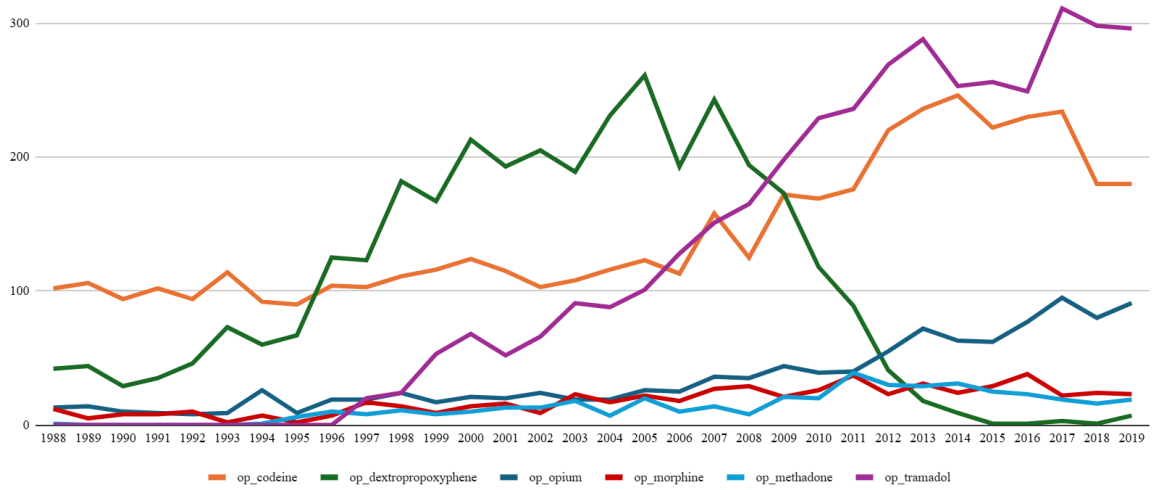


Figure 25. Different opioid exposure cases over the years

4 Discussion

4.1 Key results

We aimed to create an epidemiological report from 1988 to 2020 based on the CIGUE database used by the Poison Control Center of Lille, comparable with international studies. To do this, we determined the key indicators to be analyzed through an exhaustive review of PubMed, a non-exhaustive search using secondary search engines (http://sciencedirect.com and http://scholar.google.com), and direct contact with certain poison control centers around the world. We mainly relied on comparable indicators, mostly defined by the AAPC annual report.

4.1.1 The calls

We observed a significant increase in the number of calls received until 2013, followed by a decline.

The most frequent caller was the family of the patient (36.5%) followed by hospital personnel (medical or paramedical) (26.4%), the SAMU (14.5%), the patient (8.2%), non-hospital paramedic staff (5.5%) and general practitioners (5%). Calls were mostly from the residence (own or other) of the patient (89.4%), from the French departments of the *Nord* (32.5%) and *Ile-de-France* (17.8%). The age category mostly concerned were children between 1 and 5 years old (46.6%).

4.1.2 The reason for exposure

Most of the calls were categorized as domestic accident (67.9%) followed by suicidal behavior (12.7%) and therapeutic accident (12.1%). The number of calls categorized as suicidal behavior has been stable over the years, and concerned mostly 13 to 20 years old, representing 56% of the calls for this age class. The percentage of calls linked to domestic accident over the years has been stable, between 63.0% in 1988 and 66.8% in 2014, concerning mostly children between 0 and 13. The proportion of therapeutic accidents has grown consistently over the years with 4.88% in 1988 to 18.84% in 2019. It's mostly children between 0 and 1 year old and between 5 and 13

years old, that are concerned with therapeutic errors. Among adults, the risk of therapeutic error increases with the age.

4.1.3 Clinical severity on call

With the introduction of the PSS in late 1993, the clinical severity on calls was implemented on CIGUE. This explains the decrease in cases with symptoms described as unknown or other. Most of the calls were categorized as asymptomatic (55%) or low to moderate (30.5%). Only 0.7% were classified as severe to lethal on call. Suicidal behaviors had the most severe symptoms on call. 3.5% of all calls concerning suicidal behavior had a symptomatology described as severe to lethal while domestic accidents and therapeutic accidents mostly remained asymptomatic or low to moderate. While the proportion of severity increased from ages 0 to 50 and generally decreased for those over 50, we observe that the symptoms on call described as severe or lethal only increased with age.

4.1.4 Substances

The substances most frequent in human exposures were household detergents with 9.1% of the cases, food (spoiled or not) with 8.4%, benzodiazepine 7.3%, paracetamol with 5.7% and solvents with 5.5%. We focused our attention on household detergents, benzodiazepines, paracetamol and opioids.

4.2 Discussion of the results

4.2.1 Decline in case numbers

The decline in case numbers since 2013 can be attributed to the widespread adoption of the national toxicovigilance software, SICAP, which was created in 2000 and has been progressively implemented across the country over the years. This software was used concurrently with CIGUE until 2020, when the last call was registered on CIGUE [63]. The decline in birth rates by 1.8% since 1988 (most of exposure cases are for children between 1 and 5) [64] and the increase of reliable internet information might also have contributed to this trend. This data is similar to other poison centers around the world [38,48,53].

4.2.2 Household detergents

Household detergents remain the number one substance for human exposure cases. These household detergent exposures concern mostly small children (< 5 years old). This trend is comparable to most international studies [38,41,42,48,53,54]. The Poison centers in France uses the BNPC to determine the composition of the product and deliver the appropriate protocol to the patient. Most of the time, these exposures remain asymptomatic. But sometimes they can be dangerous and warrant an analysis. This was the case with water soluble pods or other liquid detergents. Symptomatic cases accounted for 67% of all cases. Symptomatic exposures to pods were more frequently severe than those to other liquid laundry detergents [65,66]. In 2015, an international campaign by the OECD (Organization for Economic Co-operation and Development) and the European Commission took place from March 16 to 23 to raise awareness among consumers and parents of young children about this risk. This campaign, supported by the DGCCRF (Directorate General for Competition, Consumer Affairs, and Fraud Control) and the DGS, aimed to regulate liquid laundry detergent pods and widely disseminate recommendations to the public

regarding the use and storage of these products, as well as the appropriate actions to take in case of exposure to the liquid contained in these pods [66–68].

4.2.3 Benzodiazepines

The number of cases concerning benzodiazepines, be it for anxiolytic, hypnotic or antiepileptic purposes, has been steady over the years with a downward trend since 2013. A trend confirmed nationwide with a report of the ANSM [69]. This also can be explained with an awareness campaign for doctors in 2012 regarding the prescription of benzodiazepines and a restriction of clonazepam (Rivotril®) and zolpidem to secure prescriptions (in 2011 [70] and 2017 [71] accordingly). Benzodiazepine exposure was mostly found on patients between 13-20 years old followed by 20-50 years old. 63.7% of benzodiazepine exposure cases were categorized as suicidal behavior, followed by domestic accidents with 20.2%. Only 2.4% of cases concerning benzodiazepines were categorized as severe to lethal on call. This trend is comparable with other studies [38,41,46,48,53,72].

4.2.4 Paracetamol

Over the years, the number of cases for paracetamol exposure grew substantially, rising fivefold from 1988 to 2019. The most exposed age group was 13 to 20 years old, followed by children aged 2 to 5. The most frequent reasons for paracetamol exposure cases were domestic accident with 37.1% and suicidal behavior with 35.4% of cases concerning paracetamol exposure. Most cases were categorized as asymptomatic on call. With a growing concern on hepatic toxicity [73] and auto-medication, the ANSM has launched in 2008 a public awareness campaign, and in 2018, followed up with a public consultation that led to the introduction of "OVERDOSE=DANGER" pictograms on paracetamol boxes [74,75].

4.2.5 Opioids

The number of opioid related cases has almost quadrupled from 1988 to 2019. The most exposed patients were the 13-20 years old. 48.6% of opioid exposure cases were categorized as suicidal behavior, followed by therapeutic accidents at 24.7% and domestic accidents at 20.7% of opioid cases. Most of the cases were categorized as low to moderate or asymptomatic. Following the discontinuation of dextropropoxyphene in France in March 2011, there was an increase in calls concerning codeine, tramadol, and opium. From 1988 to 2017, tramadol exposure cases increased by 311%; codeine exposure cases by 229%; opium exposure cases by 730%. Total mild opioid (Tramadol, Codeine, Opium) cases increased by 556%, while strong opioid cases (morphine) increased only by 187%.This trend was confirmed in the 2019 ANSM report on the state of opioid consumption in France [76].

The sales of codeine (alone or in combination) increased by 62% in 10 years since 2008 in France, as have the sales of tramadol (alone or in combination: +42%) and medications containing opium powder, with a doubling over 10 years (4.2 Defined daily dose (DDD) per 1,000 inhabitants per day in 2015) [76,77].

Among the 7 countries analyzed in 2015 (Germany, France, United Kingdom, Italy, Spain, Denmark, and Sweden), considering all analgesics, France ranked 3rd in Europe (121 DDD per 1,000 inhabitants per day), behind the United Kingdom (188) and Spain (151) [77]. France also ranked second in all non-opioid analgesics and first in paracetamol consumption.

France ranked third for mild opioids: tramadol was the most used substance in 2015 (48%). Tramadol was also the most used mild opioid in other countries (representing even 98% of mild opioids in Germany), except for Sweden, which used codeine more (54%) [77].

Concerning strong opioids (morphine), France ranked last among these 7 European countries in 2015. In Europe, in 2015, the biggest consumer of opioids, both mild and strong, remained the United kingdom (Figure 26, [77]). Similarly, over the past twenty years, the United States has been experiencing an opioid crisis. Since 2009 [78], after the implementation of prescription regulations and opioid usage recommendations, improved accessibility of addiction treatment and recovery services, and research on pain, addiction and alternative methods for pain management [79–83], the trend has been downward [84]. Still, the USA remains the largest opioid consumer in the world [85,86] (Figure 27).

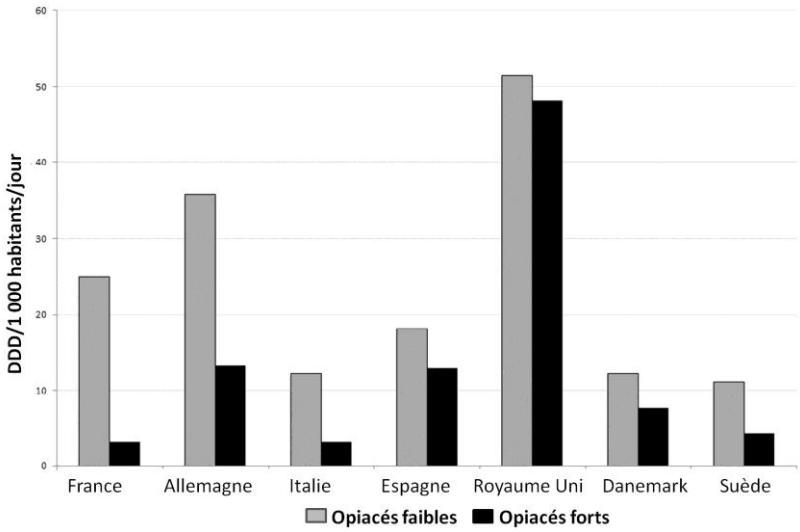
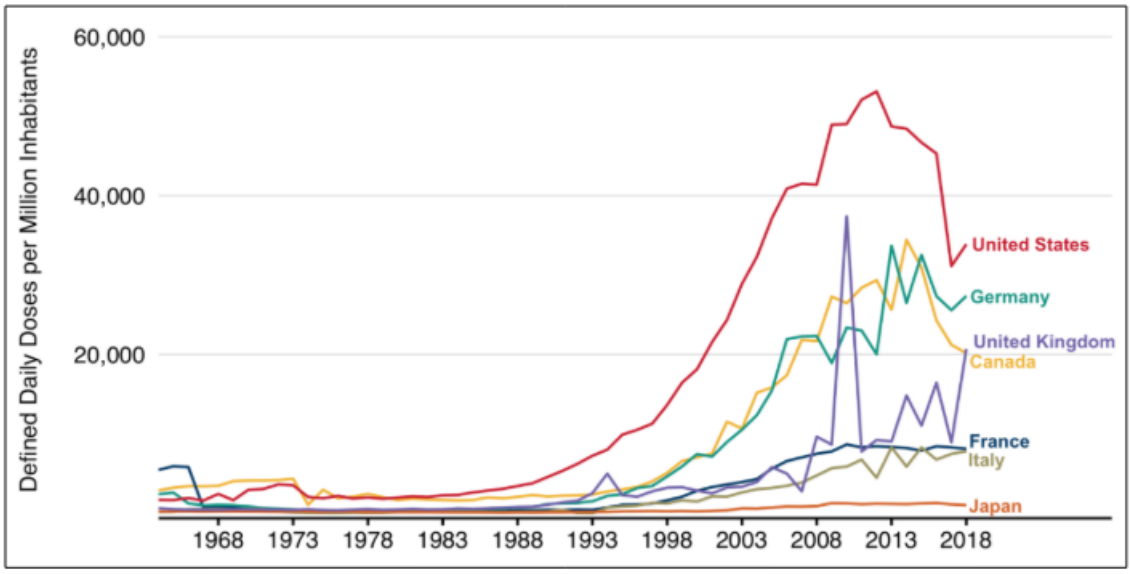


Figure 26. Opioid Consumption in 2015 in Europe [77]



Source: International consumption of narcotic drugs, 1964-2018, data provided to CRS by the International Narcotics Control Board (August 2020).

Notes: The opioids included in the total are hydrocodone, oxycodone, morphine, methadone, dextropropoxyphene, dihydrocodeine, diphenoxylate, ethylmorphine, pethidine, pholcodine, tilidine, hydromorphone, and fentanyl. Defined daily doses (DDD) are "the assumed average maintenance dose per day" for an opioid used for "its main indication in adults," according to the World Health Organization. DDDs are commonly used as a standard measure of drug use in national and international comparison studies at the population level because one DDD per day is implied. DDDs do not necessarily reflect the prescribed therapeutic dose, which is based on individual patient characteristics (age, weight, etc.). See World Health Organization, *Essential Medicines and Health Products/Defined Daily Doses*, at https://www.who.int/medicines/regulation/medicines-safety/toolkit_ddd/en/.

Figure 27. Total opioid consumption in G-7 countries (DDD per 1 million inhabitants: 1964-2018) [85]

4.2.6 Suicidal Behavior of adolescents

A troubling aspect is that suicidal behavior accounted for 12.7% of total cases, representing also the most clinically severe incidents reported. The primary age group affected was 13 to 20 years old (56% of all calls concerning this age class was for suicidal intent). This is even more evident with the analysis of benzodiazepines, paracetamol, and opioids exposure cases, where this age group was predominant, and the primary reason for their cases was suicidal intent. This trend is also confirmed by data around the world [38,41]. This can be explained in increased cases of depression, which is the number one factor in suicidal intent at adolescence [87–90]. Given the highest rates of suicidal thoughts among adolescents in France are in *Hauts-de-France* (3.8%) and *Normandy* (4.1%) [91], the Lille poison center is likely to be disproportionately exposed to cases of suicidal behavior. Unlike socioeconomic capital (measured by the economic and professional situation of the parents), which does not appear to be associated, family structure also plays a significant role, particularly for young people living in single-parent families, who are generally more exposed to psychosocial and economic vulnerabilities [91]. And lastly, the increased rate of auto-medication and availability of those medications may increase the likelihood of acting on suicidal thoughts.

4.3 Discussion of the method

This study has a solid foundation with comprehensive coverage (around 665,000 calls) over a long period (1988-2020). The analysis is based on elements described by domain experts.

While we tried to add as many indicators as we could, some were not computable: a more in-depth clinical outcome, decontamination procedures, hospitalization duration, description of fatality cases.

We tried to focus our attention on the three most common substances in human exposure cases (except food) and opioids. The analysis could have been more thorough but comparability with other studies remained one of the key objectives.

Most of international studies were presented as a retrospective epidemiological study of one year or over a predetermined period. This study remained comparable to international and French studies [38,41,48,53,69,76].

4.4 Perspectives and Clinical Significance

The CAPTV of Lille remains crucial in advising and sorting all calls related to poisonings within its area of expertise. These calls are transformed into data that can be easily analyzed. It helps us confirm or refute certain assumptions and allows us to identify trends and alert authorities to launch prevention campaigns, new recommendations, suspensions of marketing authorizations… This study, using CIGUE and its rich epidemiological data, allows us to confirm certain trends observed in the territory as well as globally, with a relatively low marginal data analysis effort.

With more time and a more thorough analysis, we could have a greater impact, whether in hospitals or in outpatient setting. With regular annual reports, we could easily identify trends and address them. Now that CIGUE no longer receives calls, we could propose a similar study on SICAP with both regional and national scope.

With the development of AI and new technologies, it is also possible to envision an assistant or software for all doctors, whether in outpatient setting or hospitals, to help them with ongoing or suspected poisonings or drug interactions. We would analyze morbidity related to drug interactions for the most prescribed medications in patients. At a time when prescription sobriety (or "deprescription") is becoming necessary, having studies and a reliable tool becomes essential.

Conclusion en Français

Le CAP de Lille demeure essentiel dans le conseil et l'orientation des appels liés aux intoxications dans son domaine d'expertise. Ces appels sont convertis en données facilement analysables, ce qui nous aide à confirmer ou infirmer certaines hypothèses et à identifier des tendances. Cela permet d'alerter les autorités pour lancer des campagnes de prévention, émettre de nouvelles recommandations, ou suspendre des autorisations de mise sur le marché… Cette étude, en utilisant CIGUE et ses riches données épidémiologiques, nous permet de confirmer certaines tendances observées à l'échelle nationale et mondiale avec un effort d'analyse de données relativement faible.

Avec plus de temps et une analyse plus approfondie, nous pourrions avoir un impact plus significatif, que ce soit en milieu hospitalier ou en ambulatoire. Des rapports annuels réguliers permettraient d'identifier et de traiter les tendances plus facilement. Maintenant que CIGUE ne reçoit plus d'appels, nous pourrions proposer une étude similaire sur SICAP à la fois au niveau régional et national.

Grâce au développement de l'IA et des nouvelles technologies, il est possible d'envisager un assistant ou un logiciel pour tous les médecins, qu'ils soient en ambulatoire ou en milieu hospitalier, afin de les aider à gérer les intoxications en cours ou suspectées et les interactions médicamenteuses. A une époque où la sobriété de la prescription (ou la "déprescription") s'impose, disposer d'études et d'outils fiables devient primordial.

Liste des tables

Liste des figures

Références

[1] Loi n° 2004-806 du 9 août 2004 relative à la politique de santé publique - Article 117. vol. 2004–801. 2004.

[2] Loi n° 2002-303 du 4 mars 2002 relative aux droits des malades et à la qualité du système de santé - Article 23. vol. 2002–303. 2002.

[3] Décret n°99-841 du 28 septembre 1999 portant organisation de la toxicovigilance et modifiant le code de la santé publique (deuxième partie : Décrets en Conseil d'Etat). vol. 99–841. 1999.

[4] Loi n° 2016-41 du 26 janvier 2016 de modernisation de notre système de santé. 2016.

[5] Arrêté du 18 juin 2002 relatif au système informatique commun des centres antipoison. 2002.

[6] Décret n°96-833 du 17 septembre 1996 relatif aux missions et moyens des centres antipoison et modifiant le code de la santé publique (troisième partie : Décrets). 1996.

[7] Bertrand M. Etude d'import/export de dossiers d'intoxication au Centre antipoison du CHRU de Lille. Université des Sciences et Technologies de Lille CUEEP, 1999.

[8] Estimation de la population au 1er janvier 2020 | Insee 2020. https://www.insee.fr/fr/statistiques/1893198 (accessed June 19, 2020).

[9] Mathieu-Nolf M. Rapport annuel de 2006 du Centre Antipoison de Lille. 2006.

[10] Marie-Odile Rambourg-Schepens, Antoine Pitti-Ferrandi, Martine Ledrans, Michel Jouan. Rapport de la mission InVS/Afsse sur les Centres antipoison et les Centres de toxicovigilance : Propositions sur l'organisation de la toxicovigilance 2003.

[11] Nisse P, Mathieu-Nolf M, Deveaux M, Forceville X, Combes A. A Fatal Case of Metformin Poisoning. J Toxicol Clin Toxicol 2003;41:1035–6. https://doi.org/10.1081/CLT-120026533.

[12] P N, C C, D P, M M-N. [Accidental ingestion of methadone and buprenorphine by children. A case review of the Lille Poison Centre between 1995 and 2005]. Acta Clin Belg 2006;61 Suppl 1:37–40. https://doi.org/10.1179/acb.2006.067.

[13] Nisse P, Lampin ME, Aubry E, Cixou E, Mathieu-Nolf M. [Fatal aorto-esophageal fistula due to accidental ingestion of button battery. Algorithm for management of disk-battery ingestion in patients younger than 6 years old]. - Abstract - Europe PMC n.d. https://europepmc.org/article/med/27546304 (accessed June 19, 2020).

[14] Garat A, Nisse P, Kauv M, Mathieu-Nolf M, Allorge D, Mathieu D. Lactic acidosis due to voluntary e-liquid ingestion. Toxicol Anal Clin 2016;28:329–32. https://doi.org/10.1016/j.toxac.2016.05.001.

[15] Mathieu-Nolf M, Mathieu D, Durak-Carpeza C, Linke JC, COQUELLE-COUPLET V. A one year longitudinal study of 563 carbon monoxide

poisonings in North of France. XX Int Congr Eur Assoc Poison Cent Clin Toxicol 2000.

[16] Raub JA, Mathieu-Nolf M, Hampson NB, Thom SR. Carbon monoxide poisoning — a public health perspective. Toxicology 2000;145:1–14. https://doi.org/10.1016/S0300-483X(99)00217-6.

[17] Manel J, Nisse P, Tournoud C, Villa C, Greillet C, Sinno-Tellier S, et al. Étude rétrospective des expositions accidentelles enregistrées par les Centres antipoison et de toxicovigilance du 01/01/2013 au 30/06/2014 Étude comparative des cas d'exposition des enfants aux mégots de cigarettes Novembre 2017. 2017.

[18] Mathieu-Nolf M. Poisons in the Air: A Cause of Chronic Disease in Children. J Toxicol Clin Toxicol 2002;40:483–91. https://doi.org/10.1081/CLT-120006751.

[19] Nisse P, Linke JC, COQUELLE-COUPLET V, Deveaux M, Mathieu D, Mathieu-Nolf M. Deaths from pesticides in North of France : 1988 - 1998. XX Int Congr Eur Assoc Poison Cent Clin Toxicol 2000.

[20] ENTIS n.d. https://www.entis-org.eu/ (accessed June 19, 2020).

[21] Mattiuzzi C, Lippi G. Worldwide epidemiology of carbon monoxide poisoning. Hum Exp Toxicol 2019:960327119891214. https://doi.org/10.1177/0960327119891214.

[22] Boedeker W, Watts M, Clausing P, Marquez E. The global distribution of acute unintentional pesticide poisoning: estimations based on a systematic review. BMC Public Health 2020;20:1875. https://doi.org/10.1186/s12889-020-09939-0.

[23] Gunnell D, Eddleston M, Phillips MR, Konradsen F. The global distribution of fatal pesticide self-poisoning: systematic review. BMC Public Health 2007;7:357. https://doi.org/10.1186/1471-2458-7-357.

[24] Peden M. World report on child injury prevention. Geneva: World Health Organization; 2008.

[25] Brissaud O, Naud J, Villega F. Intoxications médicamenteuses de l'enfant. Wwwem-Premiumcomdatatraitesug025-43645 2011.

[26] Meredith TJ. Epidemiology of poisoning. Pharmacol Ther 1993;59:251–6. https://doi.org/10.1016/0163-7258(93)90069-P.

[27] Pourmand A, Wang J, Mazer M. A survey of poison control centers worldwide. DARU J Pharm Sci 2012;20:13. https://doi.org/10.1186/2008-2231-20-13.

[28] Mathieu-Nolf M. The role of poison control centres in the protection of public health: changes and perspective. Przegl Lek 2005;62:543–6.

[29] Laborde A. New roles for poison control centres in the developing countries. Toxicology 2004;198:273–7. https://doi.org/10.1016/j.tox.2004.02.002.

[30] Krenzelok EP, McElwee NE. International Poison Information Center data collection capabilities. Vet Hum Toxicol 1995;37:246–8.

[31] WHO. Poison control and unintentional poisoning 2024. https://www.who.int/data/gho/data/themes/topics/indicator-groups/poison-control-and-unintentional-poisoning (accessed June 3, 2024).

[32] Harrison DL, Draugalis JR, Slack MK, Langley PC. Cost-effectiveness of Regional Poison Control Centers. Arch Intern Med 1996;156:2601–8. https://doi.org/10.1001/archinte.1996.00440210129013.

[33] Miller TR, Lestina DC. Costs of Poisoning in the United States and Savings From Poison Control Centers: A Benefit-Cost Analysis. Ann Emerg Med 1997;29:239–45. https://doi.org/10.1016/S0196-0644(97)70275-0.

[34] Galvão TF, Silva MT, Silva CD, Barotto AM, Gavioli IL, Bucaretchi F, et al. Impact of a poison control center on the length of hospital stay of poisoned patients: retrospective cohort. Sao Paulo Med J 2011;129:23–9. https://doi.org/10.1590/S1516-31802011000100005.

[35] King W, Palmisano P. Poison control centers: can their value be measured? South Med J 1991.

[36] Galvao TF, Silva EN, Silva MT, Bronstein AC, Pereira MG. ECONOMIC EVALUATION OF POISON CENTERS: A SYSTEMATIC REVIEW. Int J Technol Assess Health Care 2012;28:86–92. https://doi.org/10.1017/S0266462312000116.

[37] Lesko CR, Fox MP, Edwards JK. A Framework for Descriptive Epidemiology. Am J Epidemiol 2022;191:2063–70. https://doi.org/10.1093/aje/kwac115.

[38] Gummin DD, Mowry JB, Spyker DA, Brooks DE, Beuhler MC, Rivers LJ, et al. 2018 Annual Report of the American Association of Poison Control Centers' National Poison Data System (NPDS): 36th Annual Report. Clin Toxicol Phila Pa 2019;57:1220–413. https://doi.org/10.1080/15563650.2019.1677022.

[39] Land ME, Wetzel M, Geller RJ, Kamat PP, Grunwell JR. Analysis of 207,543 children with acute opioid poisonings from the United States National Poison Data System. Clin Toxicol Phila Pa 2019:1–8. https://doi.org/10.1080/15563650.2019.1691731.

[40] Manchikanti L, Helm S, Fellows B, Janata JW, Pampati V, Grider JS, et al. Opioid epidemic in the United States. Pain Physician 2012;15:ES9-38.

[41] Swedish Poisons Information Centre Annual Report 2019. Sweden: Swedish Poisons Information Centre; 2019.

[42] Dalhoff KP. Status and trends in poisonings in Denmark 2007-2009. Dan Med Bull Online 2011;58.

[43] Piekarska-Wijatkowska A, Czyzewska S, Kotwica M, Krakowiak A. [Epidemiology of acute poisonings during 2002-2011 in Toxicology Unit; Department of Occupational Medicine and Toxicology, Nofer Institute of Occupational Medicine, Lodz, Poland]. Przegl Lek 2013;70:848–51.

[44] Bateman DN, Good AM. Five years of poisons information on the internet: the UK experience of TOXBASE. Emerg Med J EMJ 2006;23:614–7. https://doi.org/10.1136/emj.2006.034181.

[45] Tormey WP, Moore T. Poisonings and clinical toxicology: a template for Ireland. Ir J Med Sci 2013;182:17–23. https://doi.org/10.1007/s11845-012-0828-3.

[46] NPIC Ireland Annual report 2020. Ireland: NPIC; 2020.

[47] Reichert C, Degrandi C, Hofer KE. Intoxications en Suisse. Bull Médecins Suisses 2022;103:510–4. https://doi.org/10.4414/bms.2022.20596.

[48] Bentur Y, Lurie Y, Cahana A, Bloom-Krasik A, Kovler N, Neuman G, et al. Poisoning in Israel: Annual Report of the Israel Poison Information Center, 2017. Isr Med Assoc J IMAJ 2019;21:175–82.

[49] Amir A, Haleem F, Mahesar G, Abdul Sattar R, Qureshi T, Syed JG, et al. Epidemiological, Poisoning Characteristics and Treatment Outcomes of Patients Admitted to the National Poisoning Control Centre at Karachi, Pakistan: A Six Month Analysis. Cureus 2019;11:e6229. https://doi.org/10.7759/cureus.6229.

[50] Andiran N, Sarikayalar F. Pattern of acute poisonings in childhood in Ankara: what has changed in twenty years? Turk J Pediatr 2004;46:147–52.

[51] Yang C-C, Wu J-F, Ong H-C, Hung S-C, Kuo Y-P, Sa C-H, et al. Taiwan National Poison Center: Epidemiologic Data 1985–1993. J Toxicol Clin Toxicol 1996;34:651–63. https://doi.org/10.3109/15563659609013825.

[52] Wu Y-Q, Sun C-Y. Poison control services in China. Toxicology 2004;198:279–84. https://doi.org/10.1016/j.tox.2004.02.003.

[53] Chow TYA, Chan CK, Ng SH, Tse ML. Hong Kong Poison Information Centre: Annual report 2018. Hong Kong J Emerg Med 2020;27:344–55. https://doi.org/10.1177/1024907919893469.

[54] Srivastava A, Peshin SS, Kaleekal T, Gupta SK. An epidemiological study of poisoning cases reported to the National Poisons Information Centre, All India Institute of Medical Sciences, New Delhi. Hum Exp Toxicol 2005;24:279–85. https://doi.org/10.1191/0960327105ht527oa.

[55] Tagwireyi D, Chingombe P, Khoza S, Maredza M. Pattern and Epidemiology of Poisoning in the East African Region: A Literature Review. J Toxicol 2016;2016:8789624. https://doi.org/10.1155/2016/8789624.

[56] Chelkeba L, Mulatu A, Feyissa D, Bekele F, Tesfaye BT. Patterns and epidemiology of acute poisoning in Ethiopia: systematic review of observational studies. Arch Public Health Arch Belg Sante Publique 2018;76:34. https://doi.org/10.1186/s13690-018-0275-3.

[57] Glaizal M, Schmitt C, Tichadou L, Hayek-Lanthois M, Haro L de. Réponse à l'urgence et toxicovigilance : bilan de 11 ans de consultations du centre antipoison de Marseille (2002–2012). Wwwem-Premiumcomdatarevues23520078v26i2S2352007814000328 2014.

[58] ANSES. Rapport d'activité de l'ANSES 2018. 2018.

[59] Dispositif National de Toxicovigilance A. Rapport d'Activité de Toxicovigilance 2017. 2017.

[60] Moradi M, Ghaemi K, Mehrpour O. A hospital base epidemiology and pattern of acute adult poisoning across Iran: a systematic review. Electron Physician 2016;8:2860–70. https://doi.org/10.19082/2860.

[61] Capaldo L, Sciaux P-E, Floccia M, Faucher A-C, Labadie M. Intoxications chez les personnes âgées de 75 ans et plus : données du Centre Antipoison

de Bordeaux entre 2010 et 2014. Wwwem-Premiumcomdatarevues23520078v29i2sSS2352007817301142 2017.

[62] Recherches n'impliquant pas la personne humaine, études et évaluations dans le domaine de la santé 2018. https://www.cnil.fr/fr/declaration/methodologie-de-reference-04-recherches-nimpliquant-pas-la-personne-humaine-etudes-et-evaluations-dans-le-domaine-de-la-sante (accessed May 15, 2024).

[63] Esante.gouv. Système d'information des centres antipoison. Agence Numér En Santé 2024. https://esante.gouv.fr/SICAP (accessed May 31, 2024).

[64] Macrotrends. France Birth Rate 1950-2024 2024. https://www.macrotrends.net/global-metrics/countries/FRA/france/birth-rate (accessed May 31, 2024).

[65] Fatoumata Rigaux-Barry, Jacques Manel, Anne-Marie Patat, Laurie Cordier. Exposure to liquid laundry pods: a retrospective study by the French poison control and toxicovigilance centres from 2005 to 2012. 2014.

[66] Scharman EJ. Liquid "laundry pods": a missed global toxicosurveillance opportunity. Clin Toxicol Phila Pa 2012;50:725–6. https://doi.org/10.3109/15563650.2012.713109.

[67] Lessive liquide : éloignez les capsules des enfants. Serv LÉtat Dans Yonne 2015. https://www.yonne.gouv.fr/Actions-de-l-Etat/Securite-et-prevention-des-risques/Risques-de-la-vie-courante/Lessive-liquide-eloignez-les-capsules-des-enfants (accessed May 31, 2024).

[68] Day R, Bradberry SM, Thomas SHL, Vale JA. Liquid laundry detergent capsules (PODS): a review of their composition and mechanisms of toxicity, and of the circumstances, routes, features, and management of exposure. Clin Toxicol Phila Pa 2019;57:1053–63. https://doi.org/10.1080/15563650.2019.1618466.

[69] ANSM. Etat des lieux de la consommation des benzodiazepines en France. France: ANSM; 2017.

[70] ANSM. RIVOTRIL - ANSM : Agence nationale de sécurité du médicament et des produits de santé 2024. https://archive.ansm.sante.fr/Activites/Surveillance-des-stupefiants-et-des-psychotropes/Medicaments-a-risque-d-usage-detourne-ou-de-dependance/Medicaments-a-risque-d-usage-detourne-ou-de-dependance/RIVOTRIL (accessed June 5, 2024).

[71] ANSM. Prescription obligatoire du zolpidem sur ordonnance sécurisée - Point d'Information - ANSM : Agence nationale de sécurité du médicament et des produits de santé 2024. https://archive.ansm.sante.fr/S-informer/Points-d-information-Points-d-information/Prescription-obligatoire-du-zolpidem-sur-ordonnance-securisee-Point-d-Information (accessed June 5, 2024).

[72] Votaw VR, Geyer R, Rieselbach MM, McHugh RK. The epidemiology of benzodiazepine misuse: A systematic review. Drug Alcohol Depend 2019;200:95–114. https://doi.org/10.1016/j.drugalcdep.2019.02.033.

[73] Boudjemai Y, Mbida P, Potinet-Pagliaroli V, Géffard F, Leboucher G, Brazier J-L, et al. Patients' knowledge about paracetamol (acetaminophen): a study in

a French hospital emergency department. Ann Pharm Fr 2013;71:260–7. https://doi.org/10.1016/j.pharma.2013.03.001.

[74] Actualité - Paracétamol et risque pour le foie : un message d'alerte ajouté sur les boîtes de médicament - Communiqué. ANSM 2018. https://ansm.sante.fr/actualites/paracetamol-et-risque-pour-le-foie-un-message-dalerte-ajoute-sur-les-boites-de-medicament-communique (accessed May 31, 2024).

[75] Graham GG, Davies MJ, Day RO, Mohamudally A, Scott KF. The modern pharmacology of paracetamol: therapeutic actions, mechanism of action, metabolism, toxicity and recent pharmacological findings. Inflammopharmacology 2013;21:201–32. https://doi.org/10.1007/s10787-013-0172-x.

[76] ANSM. Etat des lieux de la consommation des antalgiques opioïdes et leurs usages problematiques. 2019.

[77] Hider-Mlynarz K, Cavalié P, Maison P. Trends in analgesic consumption in France over the last 10 years and comparison of patterns across Europe. Br J Clin Pharmacol 2018;84:1324–34. https://doi.org/10.1111/bcp.13564.

[78] Compton WM, Jones CM. Epidemiology of the U.S. opioid crisis: the importance of the vector. Ann N Y Acad Sci 2019;1451:130–43. https://doi.org/10.1111/nyas.14209.

[79] CDC. Evidence-Based Strategies for Preventing Opioid Overdose: What's Working in the United States - Healthy People 2030 | health.gov 2024. https://health.gov/healthypeople/tools-action/browse-evidence-based-resources/evidence-based-strategies-preventing-opioid-overdose-whats-working-united-states (accessed June 5, 2024).

[80] Leshner AI, Mancher M, editors. Medications for Opioid Use Disorder Save Lives. Washington, D.C.: National Academies Press; 2019. https://doi.org/10.17226/25310.

[81] Jones CM, McCance-Katz EF. Characteristics and prescribing practices of clinicians recently waivered to prescribe buprenorphine for the treatment of opioid use disorder. Addict Abingdon Engl 2019;114:471–82. https://doi.org/10.1111/add.14436.

[82] Jones CM, Campopiano M, Baldwin G, McCance-Katz E. National and State Treatment Need and Capacity for Opioid Agonist Medication-Assisted Treatment. Am J Public Health 2015;105:e55-63. https://doi.org/10.2105/AJPH.2015.302664.

[83] Compton WM, Jones CM, Baldwin GT. Relationship between Nonmedical Prescription-Opioid Use and Heroin Use. N Engl J Med 2016;374:154–63. https://doi.org/10.1056/NEJMra1508490.

[84] Jayawardana S, Forman R, Johnston-Webber C, Campbell A, Berterame S, de Joncheere C, et al. Global consumption of prescription opioid analgesics between 2009-2019: a country-level observational study. EClinicalMedicine 2021;42:101198. https://doi.org/10.1016/j.eclinm.2021.101198.

[85] Congressional Research Service. Consumption of Prescription Opioids for Pain: A Comparison of Opioid Use in the United States and Other Countries. USA: Congressional Research Service; 2021.

[86] International narcotics drugs board. Narcotic Drugs — Estimated World Requirements for 2024 — Statistics for 2022. INDB, WHO; 2022.

[87] Bridge JA, Goldstein TR, Brent DA. Adolescent suicide and suicidal behavior. J Child Psychol Psychiatry 2006;47:372–94. https://doi.org/10.1111/j.1469-7610.2006.01615.x.

[88] Garrison CZ, Jackson KL, Addy CL, McKeown RE, Waller JL. Suicidal behaviors in young adolescents. Am J Epidemiol 1991;133:1005–14. https://doi.org/10.1093/oxfordjournals.aje.a115809.

[89] Pelkonen M, Marttunen M. Child and adolescent suicide: epidemiology, risk factors, and approaches to prevention. Paediatr Drugs 2003;5:243–65. https://doi.org/10.2165/00128072-200305040-00004.

[90] Sidhartha T, Jena S. Suicidal behaviors in adolescents. Indian J Pediatr 2006;73:783–8. https://doi.org/10.1007/BF02790385.

[91] OFDT & Santé Publique France. Tentatives de suicide et pensées suicidaires chez les jeunes Français Résultats des enquêtes ESCAPAD 2014 et ESPAD 2015. France: Santé Publique France; 2017.

Annexe 1

Table 8. Proportion of gravity over the years (p=0)

Date	Unknown / Other	Asymptomatic	Low to Moderate	Severe to Lethal
1988	99.37	0.49	0.14	0
1989	99.31	0.49	0.19	0.01
1990	99.32	0.45	0.21	0.02
1991	95.69	3.48	0.8	0.03
1992	95.44	3.7	0.87	0
1993	74.22	13.07	11.57	1.14
1994	26.1	47.73	25.33	0.83
1995	20.6	55.52	23.27	0.61
1996	20.69	57.02	21.57	0.73
1997	15.33	60.05	23.77	0.85
1998	12.31	57.57	29.44	0.68
1999	11.42	59.87	28.29	0.43
2000	11.76	54.63	32.93	0.68
2001	8.77	59.82	30.82	0.6
2002	4.41	62.24	32.55	0.8
2003	4.47	60.94	33.83	0.76
2004	5.31	59.67	34.24	0.79
2005	8.83	59.12	31.29	0.76
2006	3.99	62.93	32.51	0.58
2007	2.57	65.21	31.66	0.56
2008	2.93	62.33	34.22	0.52
2009	1.87	64.57	32.94	0.62
2010	1.76	62.62	34.88	0.74
2011	1.56	62.26	35.36	0.83
2012	1.14	61	36.95	0.91
2013	1.04	59.85	38.21	0.9
2014	1.05	60.2	37.85	0.9
2015	0.71	60.61	37.86	0.82
2016	0.55	61.26	37.17	1.02
2017	0.74	62.56	35.93	0.77
2018	0.4	61.69	36.85	1.06
2019	0.56	61.98	36.53	0.93
2020	0.94	59.68	38.38	1

Table 9. Proportion of gravity on call by reason (p=0)

PSS	Domestic accident	Therapeutic accident	Other	Suicidal Behavior	Environmentally linked	Voluntary intoxication	Criminal or Incendiary related	Work / School related
Other / Unknown	13.06	6.74	22.81	25.24	16.44	13.06	9.51	12.14
Asymptomatic	59.78	70.52	39.85	30.03	26.92	41.59	22.75	15.07
Low to moderate	26.99	22.13	33.83	41.21	55.67	43.82	66.64	72.17
Severe to lethal	0.17	0.61	3.51	3.52	0.98	1.53	1.09	0.62

Annexe 2

Table 10. Benzodiazepine cases over the years

Year	Bromazepam	Prazepam	Alprazolam	Clobazam	Diazepam	Clorazepate	Zopiclone	Lorazepam	Lormetazepam	Zolpidem	Oxazepam
1988	502	138	133	104	113	431	101	398	1	33	90
1989	227	105	78	57	45	277	84	287	21	41	53
1990	338	79	65	49	50	140	61	194	37	57	38
1991	345	76	96	39	55	126	78	156	29	62	32
1992	327	83	84	21	53	131	99	142	24	78	40
1993	466	101	153	31	69	208	136	210	45	141	50
1994	357	84	138	25	47	128	128	120	32	164	27
1995	327	85	163	23	37	190	140	124	16	156	19
1996	366	98	213	21	44	170	192	89	31	191	31
1997	312	97	171	14	34	152	173	98	27	159	26
1998	403	99	230	20	57	197	171	109	39	213	55
1999	364	67	207	17	39	145	183	81	38	197	37
2000	395	92	273	16	34	171	201	86	30	214	59
2001	355	96	237	32	38	120	140	86	44	196	46
2002	366	83	276	19	39	122	165	85	28	228	69
2003	404	99	264	22	56	128	165	99	28	267	68
2004	350	91	240	34	61	124	162	81	41	266	76
2005	359	119	212	34	43	84	166	75	47	209	66
2006	311	114	211	34	60	76	136	75	43	226	62
2007	321	118	199	43	61	83	148	98	38	209	76
2008	286	132	215	28	63	56	128	91	42	193	77
2009	288	147	211	21	80	74	135	98	46	212	84
2010	348	164	262	45	106	94	156	150	47	257	125
2011	303	122	280	49	118	94	190	166	61	269	119
2012	271	128	233	49	107	40	172	187	60	250	142
2013	271	96	343	36	143	52	165	185	74	284	172
2014	196	78	272	40	99	33	139	132	63	187	161
2015	200	69	261	46	94	28	141	143	70	210	147
2016	173	85	283	50	106	29	114	147	54	183	152
2017	153	85	258	35	109	33	150	150	54	109	163
2018	153	59	274	41	118	18	162	139	39	77	162
2019	126	62	255	53	121	15	150	152	44	60	131
2020	74	40	170	20	79	12	98	137	32	34	113

Annexe 3

Table 11. Different opioid cases over the years

Year	Codéine	Dextropopoxyphene	Opium	Morphine	Methadone	Tramadol	Total
1988	102	42	13	12	1	0	170
1989	106	44	14	5	0	0	169
1990	94	29	10	8	0	0	141
1991	102	35	9	8	0	0	154
1992	94	46	8	10	0	0	158
1993	114	73	9	2	0	0	198
1994	92	60	26	7	1	0	186
1995	90	67	9	2	6	0	174
1996	104	125	19	7	10	0	265
1997	103	123	19	17	8	20	290
1998	111	182	24	14	11	24	366
1999	116	167	17	9	8	53	370
2000	124	213	21	14	10	68	450
2001	115	193	20	16	13	52	409
2002	103	205	24	9	13	66	420
2003	108	189	19	23	18	91	448
2004	116	231	19	17	7	88	478
2005	123	261	26	22	20	101	553
2006	113	193	25	18	10	128	487
2007	158	243	36	27	14	151	629
2008	125	194	35	29	8	165	556
2009	172	173	44	21	21	198	629
2010	169	118	39	26	20	229	601
2011	176	89	40	37	39	236	617
2012	220	41	55	23	30	269	638
2013	236	18	72	31	29	288	674
2014	246	9	63	24	31	253	626
2015	222	1	62	29	25	256	595
2016	230	1	77	38	23	249	618
2017	234	3	95	22	19	311	684
2018	180	1	80	24	16	298	599
2019	180	7	91	23	19	296	616
2020	89	0	51	21	8	158	327

AUTEUR : Nom : Molho **Prénom : Harlan**

Date de Soutenance : 25/06/2024

Titre de la Thèse : Epidémiologie des intoxications médicamenteuses et domestiques : analyse de la base CIGUE du centre antipoison de Lille

Thèse - Médecine - Lille « 2024 »

Cadre de classement : *Santé Publique*

DES + spécialité : *Médecine Générale*

Mots-clés : Epidémiologie, Centre Antipoison, Intoxication, Conduite suicidaire, Opioïde

Résumé :

Contexte : Il y a peu de données épidémiologiques publiées en France. Des données comparables sont indispensables pour améliorer la prévention. Nous avons donc analysé la base de données CIGUE du CAPTV de Lille de 1988 à 2020 avec des critères comparables aux études internationales.

Matériel et Méthodes : Revue de littérature exhaustive pour déterminer les indicateurs à analyser. Analyse de la base de données CIGUE du CAP de Lille, de 1988 à 2020, avec extraction de données par requête SQL.

Résultats : Sur 662179 cas, de 1988 à 2020, nous avons observé une croissance significative du nombre d'appels reçus jusqu'en 2013, suivie d'une diminution. La tranche d'âge la plus concernée était les enfants entre 1 et 5 ans (46.6%). La plupart des appels étaient catégorisés comme accident domestique (67,9%), intention de suicide (12,7%) et accident/erreur thérapeutique (12,1%). L'intention de suicide concernait principalement les 13 à 20 ans, représentant 56% des appels pour cette tranche d'âge. La proportion d'accidents domestiques est restée stable, entre 63,0% en 1988 et 66,8% en 2014, concernant principalement les enfants de 0 à 13 ans. La proportion d'accidents thérapeutiques a augmenté de manière constante, passant de 4,88% en 1988 à 18,84% en 2019. Les substances les plus fréquentes dans les expositions humaines étaient les détergents ménagers avec 9,1% des cas, les aliments (avariés ou non) avec 8,4%, les benzodiazépines 7,3%, le paracétamol avec 5,7% et les solvants avec 5,5%. Les expositions aux détergents ménagers concernaient principalement les enfants de moins de 5 ans (65,8%) et étaient en grande majorité des accidents domestiques (91,8%). L'exposition aux benzodiazépines concernait principalement les 13-20 ans (18,6%) et était principalement liée à des intentions suicidaires (63,7%), avec seulement 2,4% de symptômes sévères à létaux lors de l'appel. Les expositions au paracétamol étaient principalement des accidents domestiques (37,1%) et des comportements suicidaires (35,4%), et concernaient principalement les 13-20 ans (26,4%). Les cas d'exposition aux opioïdes ont augmenté de 389% entre 1988 et 2017, avec une augmentation de 556% pour les opioïdes légers (tramadol, codéine et opium) et de 187% pour les opioïdes forts (morphine). Le comportement suicidaire (48,6%) était la principale raison de l'exposition aux opioïdes et concernait surtout les 13-20 ans (31,2%).

Conclusion : Les résultats obtenus sont comparables avec les études internationales et françaises et montrent des tendances assez marquées.

<u>Composition du Jury</u> :

Président :	**Monsieur le Professeur Emmanuel CHAZARD**
Assesseurs :	**Monsieur le Docteur Matthieu CALAFIORE**
	Monsieur le Docteur Ramy AZZOUZ
Directeurs de thèse :	**Monsieur le Professeur Emmanuel CHAZARD**
	Monsieur le Docteur Ramy AZZOUZ