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A brief history of toxicology in France during the last two centuries (1789–1989)

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ABSTRACT

The history of toxicology in France over the last two centuries has been marked by numerous authors who have progressively broadened the fields of investigation: initially concerned with criminal or accidental poisonings, they have also taken an interest in the environment, workers' health, doping and illicit products, the dangers of radioactivity or combat gases, the risks associated with drugs, etc. Often pharmacists, these toxicology experts were specialists in analytical chemistry and developed numerous methods to refine the detection and characterization of potentially toxic products, and to better understand the mechanisms of toxicity produced by these substances.

1. Introduction

Toxicology as a science of poisons and venoms has existed since ancient times, as evidenced by the efforts of sovereigns such as Mithridates, King of Pontus in northern Anatolia, who developed the electuary that bears his name and resulted in the famous Theriac, "the best" antidote in history, which remained widely used as a panacea until the 19th century in Europe [1,2]. Organic poisons, then mineral poisons were known and used throughout the ancient world [3], especially for criminal purposes or as weapons of war (arrows or poisoned waters). In France, it was a Paris apothecary, Guy Simon, who was charged with analyzing the products of the famous "affair of poisons" under Louis XIV, which led, in 1682, to France's first important legislation on poisonous subtances. Indeed, it was often the apothecaries, then the pharmacists who handled poisons on a daily basis, who were primarily concerned as experts. This objective of toxicology in the field of poisons has gradually been extended to the field of the impact of toxic substances on the environment of man and animals, and on the particular case of human exposure in the workplace. The 19th and 20th centuries were very productive in France in terms of toxicological research, often conducted by pharmacists. This publication sets out to explore several aspects of this contemporary history over a period of two centuries: the field of action of toxicology, the evolution of the analytical methods used and the experts who distinguished themselves in this field.

2. The field of action of toxicology

Since the French Revolution in 1789, scientists, and especially pharmacists, have been concerned with developing ways to detect toxic products. From a legal point of view, several criminal cases have been an opportunity to move this field forward. Among these, the most famous is undoubtedly the Lafarge case. On September 19, 1840, Marie Capelle, widow of Lafarge, was found guilty, with mitigating circumstances, of poisoning her husband with arsenic. But the expert debates during the trial and especially afterwards were both contradictory and inconclusive [4]. Arsenic, the "millennial poison", has in any case appeared in numerous 19th century court cases. The trial of the pharmacist Danval, suspected of having poisoned his wife, will, once again, lead to his conviction in 1878, again despite the very contradictory opinions of the experts. He was pardoned in 1902 following the progress of scientific knowledge on arsenic, and was finally rehabilitated on 31 December 1923. It is estimated that the quantity of arsenic found in his wife's body "is of no interest other than to be an indication of arsenical therapeutic treatment" [5].

Another famous trial was that of Marie Besnard accused in 1949 of arsenic poisoning 12 people, including her second husband. After three trials over 10 years, she was finally acquitted in 1961 for the benefit of the doubt. Experts were also called in for an otherwise illustrious patient of Napoleon the First. Here again, a debate has long existed and is still alive among some to support the hypothesis of her arsenic poisoning. The most recent article on this subject shows that while most experts

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today consider that this is not the case, others persist in saying that doubt is still possible in the absence of irrefutable technical proof [6,7]. Arsenic is not the only element sought by toxicologists during the 19th century: nicotine [8], white vitriol [9] and white phosphorus [10], for example, are also implicated in poisonings.

Since the beginning of the 19th century, scientists have been questioned about the risks of toxic products in the environment. In 1775, Antoine Augustin Parmentier (1737–1813) published a work on water quality in Paris and later on air quality. In 1782, he was called upon to carry out work in the church of St Eloi in Dunkerque (north of France), which required the relocation of the church's cemetery. The exhumation of corpses is indeed the potential source of serious public health toxicological problems linked to mephitic gas emanations. When the Prefect of Paris, in 1802, decided to create a Committee of Hygiene and Public Health in Paris, Parmentier was part of it and chaired it from 1807 onwards [11]. The Seine Public Hygiene and Sanitation Council also dealt with many subjects relating to toxicology. In the report of the work carried out between 1829 and 1839, one can read, for example, those dealing with the ceruse and the precursor symptoms of lead colic, the presence of copper salts in pickles or the examination of lead tanks used by bakers.

As the 19th century progressed, this Committee became increasingly interested in intoxication in the workplace. In 1825, Alphonse Chevallier (1793–1879), together with several toxicologists of the time, created the "Journal de chimie médicale" (Journal of Medicinal Chemistry) where numerous works were published on toxic substances found in everyday life, such as the use of harmful substances in the manufacture and sale of jams, or accidents associated with dyes derived from anilin [12]. Among the articles published in this journal is, for example, an article by S. Robinet (1799–1869) on the use of albumin as a counterpoison to the corrosive sublime [13]. There is also an article on a collective poisoning at the Polytechnic School by copper, or another by C.P. Ollivier d'Angers (1796–1849) by mercury cyanide [14]. The pharmacist A.L.A. Fée (1789–1874) describes the plant Caltha codua (poison named Kodoya) with which the Indians poison their arrows [15]. Anselme Payen (1795–1871) makes observations on the poisoning of flies by Cobolt (impure arsenic oxide) and the minimal risk to humans and J.B. Orfila (1787–1853) on poisoning by vomitus nut, etc. Several subjects associated with environmental problems are also discussed, such as the article by A. Payen and A. Chevallier on disinfecting cesspools [16], or another on the atmosphere in saltworks, or on toxicological experiments with chromium [17].

Around the same time, from 1829 onwards, the Annals of Public Hygiene and Legal Medicine were published. In the first issue, we can read J-P. Barruel's work (1780–1838) on the poisoning of sweets, on the causes of mortality in prisons, and on the effects of alum on humans [18]. Number 2 deals with accidents to workers cleaning sewers, the detection of asbestos and arsenic, and medico-legal observations on injuries caused by sulfuric acid. Throughout the 19th century, this journal published numerous articles on poisonings, legal expertise, sources of poisoning and ways to prevent or combat them.

However, it was not until the 20th century that many toxic phenomena were understood, such as the fact that the toxicity of copper was associated with its oxidized forms: grey-green, cuprous oxide, cupric oxide, and that tinning made it possible to avoid them. It was also in the 20th century that lead poisoning was described by doctors who were able to link lead poisoning in young children with serious intellectual deficits. Even today, we continue to discover the harmful effects of lead at increasingly lower doses [19].

The beginning of the 20th century will unfortunately also be marked for toxicologists by the use of combat gases during the Great War. From the first German attack in April 1915, combat gases were the object of all the attention of the army's Grand Headquarters. On April 22, 1915, General Joffre decided to appoint the General Manager of the Health Service to ensure the protection of troops from what he called "this new mode of terror, disease and death". Action was taken to find means of protection and to provide the army with at least equivalent weapons. Pharmacists are going to play a decisive role in this effort with their in-depth knowledge of chemistry and toxicology. The research laboratories intervene with two main objectives: individual protection and the production of aggressive agents. Professors G. Bertrand (1867–1962. Pasteur Institute), V. Grignard (1871–1935. Faculty of Sciences of Lyon, Nobel Prize in Chemistry in 1912), A. Job (1870–1928. Conservatoire national des Arts et Métiers), A. Kling (1872–1947. Laboratoire municipal de Paris), C. Moureu (1863–1929. Collège de France), G. Urbain (1872–1938. Sorbonne) joined the professors of the Faculty of Pharmacy of Paris (J. Bougault (1870–1955), M. Delépine (1871–1965), P. Lebeau (1868–1959) and A. Valeur (1870–1927)) and combined their efforts to develop effective means of protection [20,21]. In order to complete the investigations carried out on the front lines on the chemical attacks, and to supplement them with medical and forensic research, several medico-legal centers were created in June 1915. Each center was headed by a Chief Medical Officer who reported only to the General Commander-in-Chief. After each gas attack in his army group and after having carried out a survey and taken various samples on the spot, he wrote a report which he sent to the municipal laboratory. To carry out his work, he was in constant contact with the toxicology pharmacists of the divisional toxicology laboratories.

Another aspect of toxicology that has developed considerably over the last two centuries concerns the toxicity of drugs and its evaluation before they are authorized on the market. In France, proprietary medicines were only defined and regulated by the 1941 law requiring a visa to market a drug, which was later transformed into a Marketing Authorization (European Directive of 1965). The file required to obtain this authorization has continued to increase, in particular on the toxicological side, as knowledge and accidents have evolved: that of thalidomide, a drug marketed from 1957 in more than 47 countries (but not in France), for example, has led to a strengthening of teratogenicity studies. Other aspects have been considered in pre-clinical toxicity studies: genotoxicity, mutagenicity, carcinogenicity, cardiotoxicity, etc. Clinical studies have also been strengthened to assess tolerance in children or the elderly, or in identified at-risk patients. For all of these studies, efforts were made to harmonize requirements at the international level through the ICH (International Conference on Harmonization) process launched in 1990 [22]. More recently, scientists and health authorities have become interested in drug residues in food and the environment.

In addition to exposure to natural radiation, living organisms and their environment have been exposed to artificial sources of ionizing radiation since the advent of medical radiography and especially military and civil nuclear energy. Radiotoxicology, born of their consequences, is the study of the direct and indirect effects of the chemical and radiative stress of radioactive chemical elements on living organisms. It concerns pharmacists in more than one way. Thus a new chapter in toxicology will develop at the end of the 20th century and will only mature in the 21st century. It was initiated in the 1970 s [23] following the multiplication of radiopharmaceutical markers (Technetium $^{99\,m}$Tc, Thallium ^{201}Tl, Indium ^{111}In, Gallium ^{67}Ga, Iodine $^{123,\ 125,\ 131}$I, Strontium ^{89}Sr, Xenon ^{133}Xe, Chromium ^{51}Cr, Copper ^{64}Cu, Fluorine ^{18}F etc.) and their ligands (albumin derivatives in microspheres or micro-aggregates, colloids, various chelating agents etc.): HMDP, DMSA, DTPA, MIBI, etc.). In addition to the classic problems of toxicokinetics, immunotoxicity, genotoxicity and carcinotoxicity, toxicity studies also include the dosimetric estimation of patient exposure to ionizing radiation in order to comply with the fundamental principles of radiation protection set forth by the International Commission on Radiological Protection (ICRP) and the European directives that include them. These therapeutic (5%) or diagnostic (95%) radioactive drugs are now explicitly included in the French Public Health Code (Article L511–1 and amendments), which specifies that the preparation and control of generators, kits and precursor radionuclides is reserved exclusively for pharmacists with specific competence:

Radiopharmacists. (article N° 92-1279 of 8 12 1992) [24].

From the second half of the 20th century, the increasing diffusion of the use of chemical compounds, although generating progress, has at the same time generated increased risks of poisoning, in particular with the multiplication of drugs and phytosanitary, industrial and domestic products or food additives. The medical emergency situations linked to this new type of aggression of the organisms led to the elaboration of a new strategy of diagnostic, clinical and therapeutic management. Poison control centers were the first to be created, followed by the resuscitation structures in the hospital emergency services and the adaptation of the analysis laboratories of these structures for the research, the detection and the dosage of these new analytes and their products of metabolic degradation in order to inform as quickly and as precisely as possible the emergency physician facing serious intoxications to be treated and too often fatal. Hospital pharmacists, whose multidisciplinary training (metabolic biochemistry, chemical pharmacy, pharmacology, analytical chemistry and clinical toxicology) prepared them for this task, are in fact the main actors of the adaptation of analytical diagnosis to the conditions and constraints of emergency medicine. We then saw the development of methods adequate for their specificity, their sensitivity and their precision before the physicochemical means of the 21st century came to simplify both the analytical approach and their implementation in biological media (blood, urine, exhaled air etc.). For a long time, these methods remained the prerogative of highly specialized services. One of the first books to bring together selected analytical techniques that can be used in current practice was written by Professor Jean Meunier (1934 −2001) of the Val-de-Grâce in 1970. This book is in 5 parts, the first of which provides useful information on the anti-poison centers and polyvalent intensive care units in France. The others are devoted to the types of poisons to be searched for, the appropriate analytical approach with the most adapted classical hospital means of the time and the most important scientific references [25]. The following year J.P. Fréjaville (1935–2019), Chantal Bismuth (1932 – 2015) and R. Bourdon (1924–1991) published a treatise on Clinical and Analytical Toxicology, a reference for French emergency toxicology laboratories, which was subsequently completed and republished. It includes a valuable index of 15,000 commercial substances whose toxic agent is easily identifiable [26].

Poison control centers respond to the increasingly frequent needs of voluntary or accidental intoxications. Few in number in France, they bring together intensive care units and biochemical and toxicological analysis laboratories, research services, and a toxicological information center that is available 24 h a day. The first one created in Paris in 1957 was directed by Professor Michel Gautier (1923–2015) at the toxicology clinic of the Fernand Widal Hospital. In 1963, the toxic pathology center of the Edouard Hérriot Hospital was the second in Lyon. The Salvator Hospital in Marseille and the Nancy University Hospital will follow.

Apart from the above-mentioned anti-poison centers, many hospitals in Paris and in the provinces have resuscitation services, often multipurpose, which treated poisoning in emergencies and the biochemical and toxicological analysis laboratories of these structures carried out toxicological research.

Finally, a great deal of work will focus on the detection of illicit and potentially dangerous products found during sports competitions, road accidents or horse races, for example. Toxicologists have also been concerned about the risks of environmental exposure to air pollutants, especially in light of the asbestos scandal and the health hazards of gaseous and particulate pollutants in urban areas. That of the effects of heavy metals, such as mercury during pregnancy, was part of the analysis of the causes of Minamata disease in Japan. The demonstration by Japanese scientists that industrial effluents containing mercury discharged into the sea at low concentrations and not exceeding the values allowed at the time could concentrate in the food chain to values toxic to humans laid the basis for new, more protective regulations.

3. The actors of toxicology in France

Many scientists, pharmacists or not, were interested in toxicology in France throughout the 19th and 20th centuries. In terms of research and teaching, several figures stand out during the 19th century. First of all, the first worldwide course in toxicology was introduced at the Paris School of Pharmacy by an ordinance of the King on January 7, 1834, and it was Joseph-Bienaimé Caventou, discoverer with Joseph Pelletier of quinine, who was in charge of this course. Thereafter a dozen professors succeeded one another in this chair of toxicology in Paris. It is necessary to mention some of them who have marked this discipline in France:

- **Henri Moissan** (1852–1907): Nobel Prize in Chemistry in December 1906 for fluorine isolation and high temperature chemistry, Henri Moissan specialized in mineral chemistry and taught toxicology from 1886 to 1899.
- **Paul Lebeau** (1868–1959). Lecturer in toxicology at the Paris School of Pharmacy for ten years from 1908. He was especially noticed at the time of the First World War. He was called upon in 1915 following the German attacks using asphyxiating gases, starting with chlorine. With his students, he developed various means of protection and neutralization of combat gases, with the use of absorbent coals that would become an international reference. After the Armistice of 1918, he continued to be an advisor to the National Defense and continued his research on protection against toxic gases
- **René Fabre** (1889–1966): René Fabre's activity in the field of toxicology was considerable. He recognized the interest of tackling the mechanisms of action of toxicants and of closely associating biology and toxicology. In 1933, he created the Institute of Industrial Hygiene and Occupational Medicine at the Faculty of Medicine. His work in occupational toxicology forms the basis of legislation both in France and abroad. This work materialized in 250 notes and 150 general reviews.
- **René Truhaut** (1909–1994) devoted himself to the study of toxicological problems in two main directions: industrial toxicology and toxicology in the agricultural and food fields. In the field of industrial toxicology, his research focused, on the one hand, on the development of characterization and dosage techniques applied to organic solvents, aromatic amines and numerous mineral poisons and, on the other hand, on the study of their fate in the organism and the mechanisms of their action. In the field of agricultural and food toxicology, he has mainly devoted his research to the evaluation of the toxic potentialities - in particular carcinogenic - of products likely to be found either in the environment or in human foodstuffs. He has become increasingly interested in the problems of toxicological evaluation methodology, which he has very seriously perfected, establishing in particular tests for the early detection of certain toxic aggressivities.

These various professors have trained many toxicologists in France for various industries and official control laboratories.

But other personalities have strongly marked the world of toxicology:

The figure of **Jean Charles Henry Sallin** (1735–1797) must be evoked for the 18th century. Forensic medicine did not take up the question of death by poisoning until the 19th century, but this precursor deserves to be cited here: Charles Henry Sallin, doctor at the Châtelet [27]. His intervention in the case of Louis Antoine de Saint-Faust de Lamothe poisoned by Antoines-François Dérues, the great crime star of the 18th century, is a model that will inspire his successors and forms the basis of this discipline. His deductive reasoning and his quality of observation make him integrate in his autopsy analysis of an exhumed body, relevant considerations such as atmospheric conditions, seasonal influence, geographical context. and the qualities of the ground where the corpse is buried, the position of the latter and the state of the place. Sallin advocating an "exclusionary approach", he endeavors to compare

the signs of poisoning and the traces left by the poison as well as their chronology of appearance with pathologies presenting a similarity and by comparing the presumed poison with all those with which it could be confused. In the Lamothe case, he rightly excludes arsenic, belladonna, hemlock, renunculi, mandrake and opium and demonstrates poisoning by the sublimated corrosive [28].

In the 19th century the figure of M. Orfila reigns over toxicology. **Mathieu Orfila** (1787–1853), born Spanish, naturalized French in 1818, Doctor of Medicine in 1811, was a pioneering master of modern toxicology since the publication of his T*raité des poisons ou Toxicologie générale* from 1813 to 1815, professor in 1819 at the Faculty of Medicine in Paris, of which he was the Dean from 1831 to 1848, became a member of the Royal Council of Public Instruction from 1834. He was regularly called upon to provide expert appraisals, and The "Gazette des tribunaux", the most famous judicial periodical of the century in France, published numerous reports on trials, restoring the words of Mathieu Orfila to its readers. If Orfila is the master of legal medicine, he owes it first and foremost to his work and the echoes he encounters. His most important and most cited book, at least in the field of legal medicine, is undoubtedly his *Leçons de médecine légale* (1821–1823), regularly expanded (*Leçons de médecine légale, Planches, 1825*), then edited as a *Traité de médecine légale* (1847) in four volumes which impresses the medical and judicial world by its approach and its cut-out. The work includes in particular the Traité des poisons tirés des règnes minéral, végétal et animal (1814), the Traité de toxicologie générale (1815) and integrates certain aspects of the *Traité des exhumations juridiques* (1830). However, although Orfila was adulated, he was also the object of sharp criticism from several of his colleagues. Some, like Alphonse Devergie or Raspail, did not hesitate to transform their manuals or treatises into forums, as did Orfila, taking their readers as witnesses to the validity of their assertions. They expose their differences in a virulent tone [29].

Another major figure in France was **Alphonse Chevallier** (1793–1879), already mentioned. Received as a pharmacist in 1822 with a thesis on Hops, he settled in [43], place du Pont Saint-Michel where he kept his pharmacy until March 1835. He organized a research and analysis laboratory where he welcomed many students from the School of Pharmacy without asking them for any payment. He made many researches on occupational diseases: those of the printers (1835), those caused by lead (1836), those of the workers working in the factories of fulminating powders (1836), those of the wallpaper workers using arsenic green (1846), those of the copper workers (1847). Chevallier's scientific activity was great, as we have been able to count from him up to 800 notes or memoirs and 2662 reports of the Hygiene Council, but it was very scattered. He first dealt with the chemical composition of certain plants, and then became mainly interested in questions of hygiene and the falsification of food substances (coffee, milk, bread, honey, chocolate, wine, flours etc.) or medicinal substances (chicory, syrups, opium, orange blossom water etc.). He also studied the Marsh apparatus and the toxicological research of arsenic, the preparation of chlorides and hypochlorites and their use for disinfection, the mineral waters of Chaudes-Aigues, the manufacture of chemical matches, the dangers resulting from the inconsiderate use of medicines, etc., recording his results in memoirs reaching the importance of pamphlets or books.

Numerous actors contributed to hygiene and toxicology in France during the nineteenth and twentieth centuries, particularly in large cities such as Paris [30]. Even if one can criticize our choice because it excludes great scientists who have distinguished themselves in more than one way in this discipline, we would like to highlight some of them, perhaps less well known but whose impact was essential:

- **Jean-Louis Lassaigne**, (1800–1859), a chemist and collaborator of Vauquelin, professor of chemistry at the Veterinary School of Alfort until 1854, expert chemist of the Court of the Seine, a position for which he put to good use his important work as a chemist, his discoveries (delphine, cathartine, phosphoric ether, etc.) and imagined a technique of mineralization of organic matter in order to search for toxic substances. We owe him an Abstract of Inorganic and Organic Chemistry in two volumes published in 1829, numerous publications in the Annals of Chemistry and Physics between 1818 and 1849, in the Journal of Medical Chemistry, Pharmacy and Toxicology, in the medical and clinical journal, or in the memoirs of the Royal Academy of Sciences of the Institut de France. One can read in volume 7 of 1827 [31] that he developed a process for the isolation and characterization of morphine in the stomach and vomit of poisoned animals and a process for the discovery of hydrocyanic or prussic acid in a liquid where there would be only 1/10000 which he had published in the medical and clinical journal in 1824 [32]. His successor as an expert at the Palais de Justice in Paris will be F.-Z. Roussin.
- **François Chaussier** (1746–1828) began his career as a surgeon, and for ten years he taught comparative human anatomy. He then developed a passion for chemistry, which he professed in Dijon from 1774, becoming a professor in 1786 and then at the Ecole Polytechnique in 1804. Doctor of Medicine from the University of Besançon in 1784, he became a member of the Royal Academy of Medicine and the Academy of Sciences and Fine Arts of Dijon. He is then considered as one of the most famous physiology professors that he taught with anatomy for 25 years at the Ecole de Santé de Paris [33]. He will be a member of the French Institute in 1823. It was in 1790 that he presented an innovative plan for teaching legal medicine, which was at the origin of the law of December 4, 1794, which established a chair of "legal medicine and history of the art of healing" at the Schools of Health, opening the position of expert in this discipline. In 1824, he published important works that were to become landmarks, including his Manuel médico-légal des poisons, preceded by considerations on poisoning [34]. In the same year, the collection of memoirs, consultations, and reports on various objects of legal medicine were considerable methodological advances, from the opening of bodies to the identification of poisons and the errors that should not be made during the expert examination. Although he was known for his other specialties, the dictionary of French biographies describes him as a medico-legal physician [35].
- After Sallin and Chaussier, it was François **Émmanuel Fodéré** (1764–1835), who, before Orfila, made progress in forensic toxicology. A physician of very modest origin, he was awarded a doctorate at the faculty of Turin in 1786 and then became a sworn doctor of the Duchy of Aosta before joining the French Army's health service in 1792 when Savoy became French. He was a professor of physics and chemistry at the central school of Nice, then a doctor at the Hôtel Dieu and the hospice for the insane in Marseille and even a consulting doctor to the King of Spain [36]. He held the chair of legal medicine in Strasbourg from 1814 until his death. He was also responsible for the chair of public hygiene and taught anatomy and physiology. Whatever field this man of genius tackled, he excelled in it and if we honor him here for the advances we owe him in toxicology and as one of the main founders of legal medicine, he is also claimed by psychiatry as a pioneer, notably for his work on suicide and "homicidal monomania". He was previously interested in thyroid diseases, which were common in his native Savoie, pulmonary phthisis, scurvy and cholera. We owe him a Treatise of legal medicine, first published in 1798 and recast in 1813 in 6 volumes, a work far superior to what existed and which is the reference at the beginning of the 19th century [37]. Volumes III and IV constitute the second part of the treatise dedicated to criminal legal medicine, of which Chapter III is devoted to the crime of poisoning; sanitary legal medicine occupies the last two volumes. Fodéré was not only an honest scientist who never failed to pay homage to his predecessors in his numerous works, but he was also an accomplished humanist, as shown by his Essai historique et moral sur la pauvreté des nations (Historical and moral essay on the poverty of nations) in 1825, which earned him the approval of the Académie des sciences and the congratulations of Pope Leo XII [38].

- **C.P. Galtier** (18.- 1876) also deserves to be mentioned among the promoters of modern toxicology. Professor of chemistry and botany applied to medicine, then of pharmacology of medical matter and toxicology at the Faculty of Medicine of Paris, he produced several important didactic works between 1836 and 1876: the Treatise of chemical and legal medical toxicology and of the adulteration of food, drinks and medicines in two volumes [39], the first one in 1845 devoted to inorganic or mineral poisons, the second one in 1855 devoted to organic and gaseous poisons, and especially the same year, his treatise of general toxicology or of poisons and poisonings in general [40]. He proposes techniques of research and methodical isolation in the various possible environments where poisons can be found, in nature or in commercialized form, dissolved in water or any other colorless or colored vehicle, in vomit, in the intestinal tract or its tissues or in any other organ, He rejects the classification adopted by Orfila and his predecessors to adopt the one dividing poisons into inorganic and organic, which he then distinguishes according to their chemical, botanical, and zoological properties with the ambition to correlate them to the physiological effects and lesions they induce. He attaches great importance to the quality of the reagents to which he gives a large place. He often refers to Duvergie and especially to Orfila of whom he makes a systematic constructive criticism and sometimes improves their procedures and their theories.
- **François Zacharie Roussin** (1827–1894), appointed in 1858 as Associate Professor of Chemistry and Toxicology in Val-de-Grâce, was both a remarkable and ingenious teacher. A precursor of photometry, he devised a process for measuring the intensity of the color of Prussian blue under the influence of light. He invented a method of controlling the purity of chloroform by means of double iron nitrosulfides and a process for the production of cyanogen and artificial rubber. He was admitted to the Chemical Society of Paris in 1859 and later became a member of the Pharmaceutical Society and editor of the Annals of Public Hygiene and Forensic Medicine. A little later, he participated in the writing of the great dictionary of medicine and practical surgery. He was interested in the diffusion of toxins through the epidermis, in particular iodide in solution or powder incorporated in ointments and highlighted physiological phenomena that would find their application in the numerous legal medical expertises he would later carry out, 800 in 14 years. The work he wrote with Ambroise Tardieu in 1867, "Études médico-légales sur l'empoisonnement" (Forensic studies on poisoning), includes the presentation of innovative methods, the first since Orfila, notably for the detection of nicotine, and integrates physiological tests in animals, which he made an indispensable complement to toxicological expertise. He will make a striking demonstration of this in the Couty de la Pommerais case by identifying digitalis poisoning. Even if he was the object of violent criticism, it was a great step forward. Roussin was also passionate about the control of industrial waste and its recycling, in particular naphthalene, which is abundant in the by-products of coal tars and from which he made di-nitrated derivatives. This led him to his discoveries of azo dyes, essential for the cleanliness of the dye industry. These derivatives of naphthionic acid which gave rise to several patents (1875) are hailed by the great German chemist Caro as "the new product, always awaited by dyers. a new technical effect., the spark that ignites the fire, the impulsive fact.". They will be the basis of Hoffman's work [41].
- **Antoine Rabuteau** (1836–1885) was a physician, physiologist and biologist, with a degree in physics and natural sciences, and a laureate of the Institut de France in therapeutic sciences. This scientist made great progress in toxicological analysis. In 1872, he presented his work on opium alkaloids to the Academy of Sciences. But it is above all his treatise on toxicology applied to poisoning (1873) and in particular its second posthumous edition in 1887 that is significant [42]. He emphasizes the chemical analysis of liquid or solid matter rejected by the victim or collected at autopsy, which is indispensable for distinguishing poisoning from diseases presenting similar symptoms or lesions (cholera, enteritis, gastroenteritis, indigestion, digestive hemorrhages, visceral steatoses, tetanus etc.) for which he proposes detailed differential diagnoses. He also insists on the importance of urinalysis, often ignored in previous publications. He recommends during post-mortem toxicological expertises to "collect the urinary reservoir and the liquid it may contain, were there only a few drops" because one can detect "better than in a liquid or any organ of the organism the traces of a poison", a practice that he had developed in two other didactic works, a manual of urology [43] and a treatise on therapeutic elements [44], a subject that he has been teaching since 1866 at the practical school of the Faculty of Medicine of Paris.
- **Jean-Adolphe-Achille-Abraham Chapuis**, (1853–1926), distinguished chemist, director of the Société des matières colorantes de Saint-Denis which he brought to the highest level of French industry. Doctor of Medicine and Pharmacist of 1st class, laureate of the Academy of Medicine, associate professor of medicine, he taught toxicology at the Practical School of the Faculty of Medicine and Pharmacy of Lyon [45]. He was the chief pharmacist of the Antiquaille Hospice. He had defended his medical thesis in 1879 on a controversial subject at the time on the toxicity of the association of fatty substances with arsenic and that he managed to clarify while some described the aggravation of the poisoning and others, the opposite. But it is his 1882 treatise on toxicology that reveals him to the world of toxicology. In it, he develops the physiological, clinical, analytical and therapeutic aspects as well as the inventory of errors not to be made during the expertise of poisonings. In view of the success of this work, he reissued it in 1889, adding numerous contributions, including new procedures and devices and their details of use, a chapter on ptomaines, the source of so many expert errors, and exemplary reports by famous experts [46]. His work earned him the Legion of Honor in 1900.
- **François Jules Ogier** (1853–1913), chemist, doctor of science, 1st director of the Toxicology Laboratory of the Prefecture of Police from 1883 to 1913 under the responsibility of Professor Brouardel, inspector of the morgue. He was a member of the Public Hygiene Advisory Committee, Knight of the Legion of Honor (1900). Author of numerous works including his treatise on toxicological chemistry in 1899, illustrated by numerous forensic medical expertises, which is a remarkable collection of practical and important chemical methodologies all studied and controlled by his experience and offering experts not only what is observed from the effect of poisons to the autopsy but also the modes of poisoning, the symptoms and the accidents that it determines, the location of poisons in organs, as well as the properties that must be known to detect them. He has perfected the technique of Stas for extracting poisons from viscera. The method of Stas, Otto and Ogier is universally known, recognized and still used today without major changes [47].
- **Emile Kohn Abrest** (1880–1975), graduated as a chemical engineer in 1901 from the University of Nancy and obtained a doctorate in physical sciences in 1910. He was appointed director of the laboratory of the Prefecture of Police in 1913 after having been a preparator and head of chemical toxicological work. He directed it until 1944 as well as the medico-legal institute where he was professor of Toxicological Chemistry as he was at the Institute of Hygiene of the University of Paris (1924) [48]. During the First World War, he took an active part in the organization of defense against gas. Member of the Superior Council of Public Hygiene of France, he became a convinced ecologist in 1927 by analyzing the "dissemination of smoke and carbon dioxide, carbon monoxide and sulfur dioxide discharged by automobiles into the air of Paris" and demonstrated the formation of the pollution canopy at the top of the Eiffel Tower [49]. In 1930, he made a remarkable communication at the 10th Congress of Industrial Chemistry, advising against the construction of high-rise buildings. He is at the origin of very useful inventions such as the "aerodoseur" which signals emanations in the vicinity of

factories, an instrument for the analysis of blood gases and a revisited Marsh apparatus. Toxicologist and Expert Biologist of the Court of Appeal of Paris, his expert reports are numerous until 1969 and some of them are famous like the one which in 1918 allows the pardon of the Pharmacist Louis Danval in prison for 25 years accused of having poisoned his wife with arsenic, and participated in the elucidation of the mysterious death of the Belgian banker Loewenstein in 1918, the case of the deputy of Guyana Jean Galmot, the crime of Violette Nozière, the Stavisky-Prince case or the enigma of Pont-St Esprit [50]. His role in the Besnard case in 1952 was less glorious, but so was that of the other experts involved. Emile Kohn-Abrest is the author of a large number of toxicological and hygiene publications, including a précis of toxicology published in 1934, republished and enriched in 1948, then in 1955 and 1962 [51], where he details in a didactic and precise manner the toxicological expertise, from the basic notions to its general conduct, considering all the aspects and environments concerned, from the air to the ante- and post-mortem biological environments, as well as monographs for each known and newly appeared poison, their mode of identification and dosage, as well as a discussion allowing to interpret the results. Numerous learned societies are proud to have counted him among their members: Royal Belgian Academy of Medicine, Society of Public Medicine, Society of Occupational Medicine (Vice-President), President of the Society of Expert Chemists of France. His action has earned him the highest distinctions, officer of the Legion of Honor and the Order of Public Health and Academy (academic palms before 1955), but also the veteran's cross, commander of the Order of the Crown of Romania.

- **Louis Truffert** (1910–2012), a former student of the "Prytanée National Militaire de La Flèche", was fascinated by chemistry and toxicology, particularly by the study of combat gases, of which his father was a victim during the 1914–18 war. In January 1943, he joined the municipal chemistry laboratory, which was to become the Central Laboratory of the Paris Police Prefecture, where he would pursue his vocation. In 1949 he presented with Henri Moureu and Paul Chauvin to the Academy of Sciences their work on the photochemical transformation of chloropicrin into phosgene and the characterization of these two bodies [52]. Until 1985, he was president of the AARS (Association for the support of health research). Thank to this position, he wrote more than 200 memoirs, publications and studies in the field of food, industrial and housing hygiene as well as in the study and control of air pollution, the atmosphere and industrial fumes [53]. His reputation is undisputed. His numerous scientific reports, in particular to the Conseil supérieur d'hygiène publique de France, were often translated into hygiene measures and official regulations. Many of his famous publications concern acute or chronic intoxications by trichloroethylene, aromatic hydrocarbons, halogenated alkyl derivatives, turpentine, quinine, rubber substitutes. His works on alcoholism, carbon monoxide intoxication, atmospheric pollution, intoxication by metals and light alloys (selenium, lead, copper, silver cyanide, galvanized iron, cadmium, aluminum and chromium), particularly in food products and their additives, and his original work on arsenic earned him the prestigious Montyon prize of the French academy of Sciences for insalubrious arts in 1958 [54]. A respected legal expert, it was precisely his work on the fixation of arsenic in the hair that contributed in 1954 to the elucidation of the origin of the metalloid in her husband's body of the Marie Besnard case [55]. He also distinguished himself in the field of doping.

This brilliant scientist at more than a hundred years old could still speak about toxicology with authority. He had not only a well-made head, for the anecdote, he had with his wife been crowned world champion of dance in 1948.

4. Methods in toxicology

The means implemented at the beginning of the 19th century for the detection of toxic products were still very limited. Adolphe Chapuis, a toxicologist chemist, wrote that during the famous arsenic poisoning cases involving the Brinvilliers and then Madame de Montespan in the 18th century, toxicological knowledge was reduced to the following: "In water by its gravity, the poison throws itself to the bottom, it obeys, it rushes down and takes the bottom. The test of fire is no less sure; it evaporates, dissipates and consumes what is innocent and pure, leaving only a pungent and pungent material that alone resists its impression. Its effects on animals are even more sensitive, it carries its malignity in all the parts where it is distributed, it vitiates everything it touches, it breaks and burns with a strange fire and violates all the entrails" [56]. At the beginning of the 19th century, the clinical signs of poisoning, whose relevance is very controversial, were essentially observed. The idea emerged to consolidate these observations by carrying out chemical analyses. As Orfila put it in 1827, "in order to assert that there is poisoning, the man of the art must demonstrate the existence of the poison by means of rigorous chemical experiments" [57].

But everything remains to be done to meet this objective: defining the potential target organs, the methods for sampling and preserving them, the observation tools (microscope), and above all the most suitable and sensitive analytical methods. The main poisons are far from being all detectable. The search for mineral poisons is limited to cyanide compounds and 6 metals: phosphorus, mercury, copper, lead, arsenic and antimony. As for arsenic, which was very often implicated in criminal poisonings in the 19th century, researchers such as Marsh in England or Cribier in France developed more efficient devices [58]. They also searched for toxins of plant origin, mainly opium alkaloids, nicotine, atropine, strychnine, and digitalis. Chemists have been groping for a long time to select the best choice of solvents and their conditions of use.

The method developed by Stas and Otto, perfected by Ogier in 1899, is still used today to eliminate proteins, lipoproteins, lecithins and impurities by successive depletion of the biological medium analyzed (viscera, gastric or intestinal contents, various biological liquids. etc.) in an increasing alcohol gradient, and to extract all non-volatile organic toxins with different solvents in an acidic and then alkaline medium. Until the 20th century, the method of detection of poisons mainly of vegetable origin resorts, on the isolates of extraction according to dichotomous approaches, to chemical reactions producing colors more or less characteristic of the alkaloids or heterosides present or of groups of them. Many chemists have attached their names to these chemical reactions: Bertrand's reactions with silico-tungstic acid, Bouchardat's with iodinated potassium iodide, Tanred-Meyer's with mercuric iodide, Marquis' with sulfuric formol, Mandelin's with ammonium sulfovanadate, Lafon's with ammonium sulfo-selenite, Frohde's with sodium sulfomolybdate, Keller-Kiliani's with iron/acetic and sulfuric acid perchloride etc.

Before the appearance of the first colorimeters (L.J. Dubosq 1870, perfected by Ph. Pellin 1913 by a device allowing measurements in monochromatic light) [59], the eye is the principal tool of observation. Ranges of controls carried out under the same conditions allow in certain cases by comparison a quantitative estimate. For mineral poisons, until the beginning of the 20th century, the chemical mineralization of biological media was carried out by calcination or by chemical oxidation using potassium chlorate and hydrochloric acid, a process known as chlorine due to the German chemists Fresenius and Babo, modified by Ogier, or the sulfo-nitric mixture recommended by Armand Gautier (1876) or Denigès (1901), and perfected many times, in particular by Truffert, who added perhydrol, or Kahane who added perchloric acid. Later on, mineralization could be done directly in the measuring apparatus (graphite furnace of atomic absorptiometers for example). But before this, the sulfides are formed by the action of gaseous or chemically produced hydrochloric acid. The sulfides are then

identified by their characteristic colors (Zinc/white, Arsenic/yellow, Antimony/orange, Manganese/pink, Chromium/bluish green, Aluminum/colorless and black for most of the others) and by various chemical reactions more or less frustrated and imprecise to allow a reliable quantification.

In the twentieth century, the means of observation and measurement of these chemical assays are improving, then it is the turn of the processes of separation and isolation of poisons and their robotization to progress, in particular liquid-liquid extraction (LLE), extraction and micro extraction on solid support (SPE, SPME) with the appearance in the late 1980 s of polymers with molecular fingerprints [60], the use of SPE / immunosorbents will arrive only in the late 1990s.1990 s. At the same time, the arsenal of liquid and gas chromatography is diversifying (injection modes, columns, detectors etc.), as well as the physico-chemical detection techniques concerning inorganic toxics (polarography, arc and spark spectrometry, flame photometry, emission or atomic absorption spectrometry, inductively coupled plasma linked to mass spectrometry (ICP/MS), mass spectroscopy of isotopic ratios, X-ray fluorescence, neutron activation etc.). The detection and determination of toxic substances has also benefited greatly since the 1970 s from immunochemical methods (EMIT, ELISA, FPIA, Radioimmunology etc.). Today, the expert toxicologist has extraordinary tools for the isolation, detection and analysis of poisons, the main one being mass spectrometry and its various variations, which have revolutionized the detection and determination of organic toxins. A few grams of viscera or a few microliters of biological fluid are enough to identify and quantify less than a billionth of a gram of toxic substance. The current list of poisons includes more than 300,000, including new drugs and especially medicines, by far the primary source of intentional or criminal poisoning. But interpretation of the data is sometimes tricky [61]. Among the substances searched for in the framework of forensic science, drugs account for more than 80% of the inventory. Apart from alcohol, which is often present in conjunction with other toxic substances, and carbon monoxide, the rest are made up of narcotic substances (the most frequent), pollutants, particularly pesticides, metals, gaseous or volatile toxic substances, cyanides and derivatives, metals or metalloids and their salts, and plant toxic substances [62].

5. Conclusion

The history of toxicology since the French Revolution of 1789 has been influenced on the one hand by events in society: criminal or accidental poisonings, toxicity of new drugs, environmental accidents for example, and on the other hand by recognized experts in this field. The latter have progressively developed methods for the detection and characterization of toxic substances with increasingly sophisticated analytical tools. However, toxicologists have also learned to be wary of hasty conclusions, as was the case in high-profile trials where the mere presence of arsenic in the viceroys of a corpse was sufficient to conclude that the victim had been criminally poisoned. Other factors were progressively taken into account in the experts' conclusions. This French toxicological expertise was often recognized at the international level in the 19th and 20th centuries and led to useful collaborations between countries, such as the ICH process, which attempts to harmonize the studies to be carried out in the different countries to ensure the safety of new drugs and avoid their unnecessary repetition.

Author statement

Both authors have worked together on each part of this publication. Bruno Bonnemain.

Declaration of Competing Interest

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

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