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Review Article

A Primer on Systematic Reviews in Toxicology

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Abstract

Systematic reviews, pioneered in the clinical context, provide a clear, methodologically rigorous and reproducible tool for summarizing the available evidence on a well-defined research question. As an established method in many research fields, systematic reviews are attracting more attention as a potential tool for answering toxicological questions. In the larger context of evidence-based toxicology, the benefits and barriers, including ways to adapt and adopt toxicology systematic reviews, will continue to be explored. To provide the toxicology community with a starting point in conducting or understanding systematic reviews, we have summarized the guidance documents available from various areas of use. We have described the systematic review process by dividing it into ten steps, starting with project planning, framing the question, writing and publishing the protocol, and ending with interpretation and reporting. In addition, we have identified methodological challenges related to toxicological questions and summarized how these can be addressed. Finally, this is the first project to stimulate scientific discussion on the issues identified to promote the development of toxicology-specific methods and encourage the use of systematic review methods for toxicology questions.

Key words: toxicology; evidence-based toxicology; methodological challenges; poisoning in living

Introduction

Today, toxicology is not the study of poisons, it is a lot of information in one breath. Also refer to Webster's Dictionary. Science has left the word writer behind. Toxicology is the study of the interaction of substances (drugs, chemicals, food, polymers, pesticides, etc.) with the biological system and its responses. In simpler terms, it is the study of changes in a living organism, especially its various organs, when exposed to a chemical substance in different doses. The word "poison" has lost its meaning today [1]. The Poisons Act was passed in 1918, and a lot has happened in science since then. Centuries ago, Paracelsus, the father of toxicology, said: All substances are poisons. Nothing is not married. The right dose separates the poison from the cure. According to ancient Sanskrit nectar (amrit and extract martio or death) is poison if consumed in large quantities. This has become very evident in recent times. The response is dose related, and a substance that works well as a cure at low doses can become toxic at higher doses. Mercury and arsenic were two popular remedies for many ailments in the early days of allopathy [2].

Today, no country allows the introduction of new drugs containing mercury or arsenic without a toxicology review. In addition to the usual reactions, many substances can cause unwanted reactions with prolonged use. A good case in point is hexachlorophene, which has been widely used since 1945 as a mild sexicide in talc and soaps. In the 1970s, hundreds of children in France were infected and more than 30 died after using talc containing five percent hexachlorophene. In fact, this substance was cleared after the little research required and given to mice for 30 days. In re-evaluating the toxicity of the substance, it was found to react with the brain and spinal cord [3]. It interferes with mitochondrial disease which leads to the destruction of myelin (the covering of the nerves) which leads to seizures, seizures and coma and death. Later, the use of this substance in cosmetics was banned in many countries. The role of the toxicologist is clear from the above paragraph. His job is to study all the positive and negative effects of a substance (medicine, insecticide or any other substance), especially considering the end of its use. He needs to determine the safe dose and the toxic dose. If the medicine is to treat a disease, the margin of safety, or the distance between the safe dose and the toxic dose, must be very large, if not perfect, for example a disease that cannot be can be treated like cancer.

A toxicologist is often tasked with collecting safety data or non-toxicity data. Chemistry is a speculative science, or science, because humans

cannot use experiments with unknown substances [4]. All toxicology research begins with rodents, even rats and mice. This defect occurs in large animals such as dogs and monkeys when appropriate. Results from animal studies must be extrapolated to humans, and this is a very difficult task, due to the large differences in organ systems between humans and animals. Toxicology can also be defined as the science that describes the safety of substances. This science is a combination of many disciplines, all of which say that his study can make him a toxicologist. The doctor you call as soon as the child eats his mother's condition is a clinical toxicologist (not available in India) [5]. Most of the cases of poisoning by anaesthesiologists are done here, even in the leading hospitals. Poisons and drugs are a small area of a toxicologist's research.

A pharmacologist who performs clinical reviews of drugs acts as a toxicologist if adverse reactions are identified. The basic sciences of toxicology are biology, pharmacology, pathology and mostly, chemistry. The toxicologist, who investigated the cause of disease, played an important role in the early development of toxicology. Statistical probability is an important element in prediction, and the role of biostatistics in toxicology cannot be ignored [6].

Importance Of Toxicology

Since toxicology is the science that determines the toxic parameters of substances or substances. Typically, toxicologists and regulatory agencies should work together to implement educational efforts in private institutions. This development itself is of great historical interest. The years after 1950 saw great growth in the chemical industry and the production of various chemicals and chemicals for human consumption such as DDT, organophosphorus pesticides, and many pesticides. new, polymers, etc [7]. About 500 to 1,000 chemicals are added to the market without proper inspection each year. In 1962, a little-known woman, Rachel Carson, wrote her memoir Silent Spring, which was necessary to make the American public aware of the seriousness of the widespread use of many of these substances. This book is great, and it started the environmental movement in America. It is a disaster for the Federal Republic of Germany, other European countries and England [8]. Thalidomide was discovered as a contraceptive drug for pregnant women in 1954 by Grunthal Chemie in Germany and the Distillers Company in England, and has many names such as Distaval, Countergan, etc. A large number (4000-5000) has been modified. Infants born prematurely who alerted the medical profession and toxicologists followed severe reactions to thalidomide taken at seven weeks of pregnancy. Other toxicological studies on animals have shown that thalidomide is a teratogen, or a substance that causes damage to the fetus[9].

The US Food and Drug Administration revoked the import license for this drug, not because of teratogenicity, but because of suspected nerve damage. These two events caused a sudden change in public opinion towards the chemical industry. These disasters and chemical disasters have led to the perception that the chemical industry is the cause of all environmental disasters. The incidents at Orange, Soso, and Times Beach, Missouri were all events that shook the American public's faith in the chemical industry [10]. All these studies have been followed by a large number of toxicological studies. Toxicology, as such, is a science that cannot live in an ivory tower. Enforcement agencies should establish safe zones. illegal entities that violate borders; Industry challenges boundaries. and the general public for more information. It can be said that toxicology is a science "for the people by the people". The widespread involvement of toxicology in all aspects of human life and its influence on the adoption and implementation of laws has led some to consider toxicology a serious problem. can't be left to the experts alone. Gerhard Zebinden, a renowned toxicologist, sums it all up when he says "you can tell a toxicologist by his appearance" [11].

History of Toxicology

Toxicology predates humanity and has many stages in its history. And to be fair to the author, the early days of toxicology began with a focus on plant and animal toxins.

THE EARLY ERA: Ancient civilizations, the Hindus, the Egyptians and the Greeks were not particularly concerned about poisons. The mysterious poison of the hemlock god was the gift of the Greeks. Aconite is the poison arrow of the Chinese and peyote, which was worshiped by the Indians of South America. Hippocrates was the first to introduce the basic principles of toxicology around 400 BC. He gave some tips to avoid taking the poison [12].

THE MIDDLE AGES: It seems that the royal families of the Middle Ages were obsessed with poison. As in many of Shakespeare's plays, Sam appears as an integral part of the stage, as a political tool and guardian of the social good. Poison is about to play, complete with unwritten rules of honor and the courage of the chosen one. Catherine de' Medici (1519-1589), the Italian queen of France, rose from this place. He is considered the first human toxicologist. Under the guise of treating the sick and the poor, Catherine tested poisonous drugs on humans. Pay attention to the speed of the onset of action, the effectiveness of the substance, the effect on different parts of the body and the complaints of the victims. But among them all Maren stood out as a visionary and expert in medicine and poison - Philippus Aureolus Theophrastus Bombestus van Honheim, simply Paracelsus (1541-1490). He challenged the Aristotelian concept of divine intelligence governing the universe. Paracelsus sees the human body as a combination of many existing elements. His major contribution to toxicology was the definition of a toxin, a chemical entity, and the relationship between chemical structure and toxicity. Paracelsus believed that there was a dose-response relationship that could be proven experimentally. He also distinguished between therapeutic (healing) and toxic effects, and the specificity of action of substances. Its interests are very broad, and there are many new types of toxins. Even in the 20th century, many medical historians have failed to measure Paracelsus' lasting contribution. According to one writer, Paracelsus was the first to make toxic magic and medicinal magic a science [13].

Till the middle 20th century:

Mathieu Joseph Bonaventura Orfila (1853-1787), a Spanish cat doctor who held a respected position at the court of Louis XVIII, was the first chemist to recognize toxicology as a new discipline and wrote a monograph called The Study of Poisons or General Toxicology in 1813. He was a chemist who introduced analytical methods to investigate the cause of murder and suicide. With the advent of the dissection approach to autopsy, loss was gradually lost as a cause of death. Orfil became a professor of law at the University of Paris. He was a pioneer in toxicology. Meanwhile, many others, such as François Magendy (1855-1783), a famous agronomist, were interested in studying the mechanism of action of ametine and strychnine. His enthusiasm spread to his students, including the famous agronomist Claude Bernard (1878-1813). He used toxicity as a tool to analyze the agronomic aspects of organic systems. Bernard's research on curare identified arrow poison as a ganglionic inhibitor. Strychnine, a bitter alkaloid from the nut of Nux Vomica. and the carbon monoxide-hemoglobin ratio is an important parameter in toxicological studies. In the 20th century, Loris Levin (1854-1929) published a textbook on toxicology. Another famous study is Dr. Ramnath Chopra's excellent book on Indian medicine from 1933. In the beginning, there was a tendency to treat poisons as part of traditional medicine. But with all the developments and tragedies, it didn't take long for the poison to attract public attention. Poison has now become a misused political term [14].

War And Toxicology:

Rapid development in all implemented sciences owe significantly to wars-Fermi's nuclear chain pile on a Chicago to college tennis courtroom docket in 1942 inside a span of in twelve years have become a devastating weapon of PE destruction at Hiroshima and in every other 5 years p~ a

supply of strength withinside the first nuclear electricity plant withinside the U.K. Did toxicology too get its proportion from the wars? The use of chemicals during World War I from 1916 to 1918 prompted scientists to study the toxicity of various compounds and synthesize other toxic substances. When using any of these compounds, keep the medicine as a substitute if possible. The toxicity of phosgene used by the Germans in 1916 was well studied at the time, but the method of operation was mistakenly attributed to the acidification produced in the system. When air masks were introduced, compounds absorbed through the human skin were considered to be secretory irritants such as lewisite (named after the inventor, Professor Lewis) or 2-chlorovinylarsine, and sulfur and nitrogen mustard [15]. Good work on the action of lewisite on the human body by Karl Vogtlin and his colleagues in 1924 led to the discovery of dimercaprol as a famous English anti-lewisite drug by RA Peters and colleagues in 1945. development during World War II (1939-1945), especially in organic phosphorus chemicals and toxins. Gerhard Schrader at Bayer, Germany and Prof. B.C. Saunders at Cambridge was in a neck-and-neck race to produce the most toxic phosphonates, or nerve gases. By the end of the war in 1945, Bayer was able to introduce a variety of organophosphate insecticides, starting with the highly toxic tetraethyl pyrophosphate, parathion, sheradan, and others, gradually reducing mammalian toxicity. by moving to the carbamate insect toxin [16].

The development of drugs against nerve gases is very good. When it was recognized that nerve gases inhibited cholinesterase, attempts were made to restore the inhibitory sulfur with exogenous activators. A lack of comparative logic and other sound led Wilson and Nachmanson in 1956 to synthesize and test the effect of pyridine-2-aldoxime hydrochlorides (2 PAM-Cl) and atropine [17]. Until today, this 2 PAM-Cl still holds the field, although its great potential is not fully understood, when Alfred Hoffmann described a new type of hallucinogenic compound, lysergic acid diethylamide (LSD, c. 1943), the attraction of this heart is true. public attention. Some Pentagon scientists thought this was the best combination of weapons and weapons, but he ignored the difference in human type and psychology. Many natural compounds have been isolated and few psychoactive substances have been synthesized in this field. These types of relationships have become big business these days and are social poison! However, no one can blame toxicity for that [18].

Role of Toxicology

Toxicology affects human life from conception in the womb to the last stage of life. There are chemicals that can damage the bread just like the eggs. Teratogenic substances harm the fetus. Infants may die from substances ingested by the mother. In the past, diseases, such as Alzheimer's disease, were considered bad aluminum and could not be avoided by eating, even if cooking was done in gold utensils. Aluminum is abundant in soil. All vegetables and herbs are high in aluminum[19]. Unfortunately, even among educated people (not only in India but in developing countries) there is a general perception that exposure to any substance in any dose is a constant thought and concern. This is exacerbated by industrial chemical accidents that have resulted in many deaths. Hungry media and some media-seeking scientists who present themselves as doomsday evangelists contributed to the problem. Amazingly, the analytical tools and techniques have increased and we can detect quantities as small as 10-9 or 10-12 grams [20].

Ignoring the harsh reality that we no longer live in a pure world, these scientific discoveries become a social and political problem that is about to throw people into a frenzy. When emotion takes the place of logic and reason, science cannot prove the truth. Here the important role of the toxicologist is to assess the potential for chemical toxicity gathered by in vivo studies based on appropriate tests or in vitro model systems [21]. Quantitative and quantitative data and using limited scientific data, predict the likelihood of adverse effects in humans using animal data. Also, scientists who shout "wolf" at all the rats trying to get the headlines can't improve the world. Again, this should be handled well by a licensed toxicologist. The study of toxicity can be done on a systemic and causal basis. Therefore, we have systemic toxicity, including toxicity of the central nervous system, liver, kidneys, respiratory system and vision of the eyes. This research includes the protection of each of these appropriate systems against chemical attacks, reactions and foreign reactions, as well as damage caused by excess [22].

Scientific research focuses on drugs, pesticides, food additives, chemicals, heavy metals, polymers, radiation, chemical carcinogens, teratogens, etc. It is difficult to generalize, and many aspects of different species must be studied individually before conclusions can be drawn [23]. The use of toxins for practical purposes can be divided into three categories, which are not simple, but flexible and overlapping. Many other classifications and names have been suggested by various authors. If standard methods cannot predict toxicity in humans, predictions should be based on chemical and physical properties, relationships between molecular structure and biological activity, pharmacokinetics, and others [24]. "Comparative toxicology" is a study of different animal species to assess their proximity to human systems. Toxicology or ethnotoxicology is a developing field that has recently focused on dubious phenomena. Drug-related toxic reactions are more common in some states or countries. This review analyzes various factors such as climate, dietary patterns, genetic factors and other environmental influences that explain these differences in the human body's response to a foreign substance. A long chapter on "political toxicology" and other terms "biopolitics" could be added. Many of the problems facing the toxicologist are not scientific or technical, but political, psychological and social. Toxicology results can be falsified by any of the above authorities to suit their purpose. A well thought out toxicologist once said that "toxicity becomes a dull study when greed and ignorance are taken away from people"[25].

Factors Modifying the Action of Poisons [26-28]

Amount/dose: The higher the amount, the more severe the toxic effects.

Form

i. Physical state: Air and vapour react faster than water. Liquid poisons work faster than solid poisons, and fine powders work faster than solid poisons.

ii. Chemical composition: The effectiveness of the poison depends on the solubility or inertness resulting from the chemical composition, e.g. AgNO3 and HCl are highly poisonous, but when combined they form the insoluble salt AgCl, which is harmless.

iii. Mechanical combination: The effect of the poison is changed by mechanical combination with neutral substances. Oxides act as catalysts when diluted in water.

Route of administration: depending on the rate of action: inhalation as gas/vapour > injection into (IV) > injection into muscle (IM), subcutaneous and intradermal > application to wound > application to serous surface > ingestion > oral introduction Maori. , for example. Rectal, rectal, urethral and sublingual > use on unbroken skin (eg nicotine patches). ('>' indicates speed of action) As a rough estimate, if the oral active dose is a unit, it will be 1½-2 times the therapeutic dose, and ¼ the subcutaneous dose.

Condition of the patient

i. Age: The toxicity is better in both cases. A child has not yet fully developed drug-absorbing enzymes and an effective blood-brain barrier, and is therefore more susceptible to the side effects of most drugs.

ii. Health status: A healthy person has better tolerance than a sick person. General illness, age, chronic illness, or debilitation may cause more lethality than a safe dose, for example. Opium in bronchial asthma and mercury in chronic nephritis.

iii. Sleep with poison: If you sleep soon after eating poison, the effect of the poison will be delayed. If the poison is consumed while drunk, the process will be delayed.

iv. Tolerance and self-awareness: Individuals are different, but tolerance can build up to a substance, so that the effect of that dose is not the same as the beginning, for example. Alcohol, barbiturates, amphetamines, benzodiazepines, tobacco and the morphine-heroin-methadone group. The other way around is the specific situation, where there is a strong reaction to drugs or food, symptoms such as dyspnoea, tremors, fever, diarrhea, bleeding, and albuminuria. Penicillin, aspirin, cocaine, sulfonamides, serum, certain foods, for example. Mushrooms, fruit, ice, fruit and heroin.

v. Stomach conditions: The presence of food in the stomach slows down the action of the poison in most cases. It also dilutes the concentration of ingested poison.

vi. Accumulation: Toxins that are not easily eliminated accumulate in the body if they are consumed continuously causing symptoms when the concentration reaches a threshold.

Diagnosis Of Poisoning in Living [29, 30]

No single symptom or group of symptoms is definitively indicative of poisoning. Symptoms often appear immediately after consuming food or drink. In cases of poisoning, these symptoms tend to persist and worsen rapidly. If multiple people who ate or drank the same food or beverage experience similar symptoms simultaneously, it can be a strong indication of poisoning. Additionally, the detection of poison in consumed food, vomit, or stool is a definitive sign of poisoning.

Symptoms Of Poisoning [31]

Sudden abdominal pain, accompanied by nausea, vomiting, diarrhea, or constipation, may signal poisoning. Sudden pallor and pupillary twitching can also be early warning signs. Unexplained coma, particularly in children, and in adults with a history of depression, may be indicative of poisoning. Rapid onset of peripheral neuropathy, such as a sudden arm drop, and quick development of gastrointestinal or neurological diseases in individuals exposed to chemicals, are concerning symptoms. Other signs include delirium, dilated pupils, paralysis (especially of the lower motor neuron type), jaundice without liver cell failure, oliguria with proteinuria and hematuria, and persistent cyanosis.

Symptoms Suggest Chronic Poisoning [32]

Symptoms worsening after the administration of food, water, or medications. Behavioral changes, such as boredom, cachexia, depression, and mood deterioration, are common in affected individuals. Nausea and vomiting are also frequent symptoms. If symptoms disappear upon removing the patient from the toxic environment, poisoning may be the cause. Toxic substances can often be detected in bodily fluids like urine, blood, feces, or vomit.

Index of Toxicity and Laboratory Determination

The toxicity of chemicals should be assessed in laboratory animals. These preliminary studies should be designed to provide as much information as possible to predict human toxicity. For any substance, there are three stages to produce a response: the exposure stage, the toxicokinetic stage (absorption, distribution, metabolism, and absorption), and the toxicodynamic stage (chemical reactor interaction). Chemicals can enter the human system in three ways: through the nose (inhalation), mouth (ingestion) and through the skin. When it is a medicine, it can also be given by injection, that is, injected into it. It can be injected subcutaneously (just under the skin), intravenously (into a muscle and directly into the bloodstream) and intramuscularly (into the muscles). In experiments with small animals, it is given in the space or inside. In each of these ways, different effects are produced. In normal practice, responses occur in different ways so that the differences can provide clues to the activation of the substance. Three types of acute effects or a single laboratory animal test are performed. Short-term or long-term trials involve giving doses once a day for 90 days and old studies related to the organization for more than 90 days (up to one year) [33].

Specific tests: (a) enhancement with other substances, (b) effects on fertility, (c) teratogenicity, (d) mutagenicity/carcinogenicity. If the substance whose toxicity is to be determined is a gas, vapor, aerosol, or dust, the lethal dose must be calculated differently. It can be displayed in static or dynamic systems. Sodium concentration is important when an animal is exposed to a certain concentration. Therefore, for information purposes, the toxicity index is denoted as LCT50, or the lethal concentration time to kill 50% of the animals used. This amount is expressed in milligrams per liter, multiplied by the exposure time per minute [34].

The War Within the System

No living organism will accept a chemical without fighting it, and the toxicologist must understand how the biological system reacts to a chemical. The tests mentioned in the previous chapters record what happens after the substance overcomes the body's defense system and enters a system. But from the time it comes into contact with a substance, a series of events occur that involve the body's "war" with the "bad" substance. The way it enters the human system is through the nose, mouth, or skin. Once ingested, the substance must enter the bloodstream, be distributed to the tissues, metabolized, stored in the tissues, and excreted in the urine or fece. These three functions are (a) penetration, (b) distribution and broadcasting, and (c) degradation. The effects of a toxic substance depend on these three steps and only become apparent when the substance reaches the site of action, it can act as an enzyme, a receptor, or a cell [35].

Peripheral Defences: Sneezing and coughing are two ways to get rid of unwanted substances in the breathing air, and are controlled by the respiratory system. A large amount of nose and eyes when exposed to chemical pollution is a way to clean it out of the body. It also helps in the hydrolysis of chemicals. Initially the breathing rate is reduced to reduce the intake of the irritant substance. Nausea and vomiting may occur, especially when taken orally, as the body tries to remove the toxic substance. Rectal cleansing is also possible. Excessive sweating is another way to flush out chemicals [36].

Absorption through Skin: The most important physical barrier to protect the body against chemicals is the skin. The keratinized skin, dermis and corium contain a high lipoid (fatty) barrier. Transport through the skin is a common process, and in this process oil-based chemicals are more efficient than water-soluble chemicals. When an ant or mosquito bites a person on the skin, the body immediately reacts with a slight swelling and collects body fluids to wash away the poison to prevent it from spreading. The skin also contains hydrolytic enzymes that can break down certain chemicals. Skin permeability varies between animals and humans. The closest skin-producing animals to humans are pigs and guinea pigs. DDT's effectiveness as a contact poison in insects is due to its absorption into the insect's exoskeleton. Human skin is therefore less toxic [37].

Lungs: Acidic substances and toxic nutrients are absorbed directly from the lungs. Cilia (hairs) in the nostrils are a physical barrier to particles larger than ten microns. Particles smaller than one micron are inhaled or dispersed into the alveoli. Particles can be removed by mucus through the glottis. Toxins that reach a cell in the lungs are absorbed directly into the bloodstream. They can also travel through the bronchi into the gastrointestinal tract, including the lymphatic system. The lung has a large surface area (50-100 square meters), has a high blood flow and is close to the outside air. In this way, it is an important organ in detoxification [38].

Gastro-intestinal Tract: A major route for the absorption of toxic substances is through food and water, and this is the most toxic route for children. The absorption of toxic substances can take place through the

digestive system from the mouth to the stomach. For example, vasodilators such as nitroglycerin are prescribed as oral capsules that are taken by mouth. Enemas are given through a syringe. Before being absorbed, toxic substances must meet with many enzymes, different pH, such as high stomach acid, intestinal microorganisms, etc. Fat-soluble substances are more easily absorbed, while water-soluble substances are absorbed from the intestine [39].

Distribution: Toxic substances must enter the bloodstream and be distributed throughout the body. That's why the drugs are injected to have a quick effect. Chemicals can be stored in various tissues and enter the bloodstream. Carbon monoxide has a strong affinity for hemoglobin. Lead is stored in the bones. Storage tanks can prevent poisoning, although the life of the poison in the system may be longer. Protein binding is one of the ways of storage in the body and is very important for toxicity assessment. For example, antipyrine is not bound at all to proteins in plasma, while secobarbital is 50% organ bound and thyroxine is 99.9% bound. In the treatment of preterm infants, penicillin-sulfonamide combination therapy was found to have a high mortality rate. When examined, it was found that the penicillin-sulfonamide mixture binds to plasma albumin, displaces the normally bound bilirubin, and flows into the brain, causing brain damage and death. Switching to tetracycline prevented this problem. The liver and kidney have the ability to remove many toxic substances from the blood. Also, body fat stores toxic chemicals like DDT and prevents them from harming humans. The blood-brain barrier prevents non-fat-soluble toxic substances from entering the brain, an immune system. This barrier is not developed at birth, and exposure to morphine and lead in infants is high [40].

Excretion: All body secretions such as tears, sweat and milk try to eliminate toxic substances, but the kidneys and liver are the two main organs for elimination and elimination. Kidney and liver function tests are important for toxicologists to assess chemical injury. It removes all toxic substances by passive glomerular filtration or active tubular diffusion in the mixed urine. The most fat-soluble fractions are collected again and the water-soluble components are removed. Bases are eliminated in acidic urine and acidic compounds in basic urine. The administration of sodium bicarbonate to remove phenobarbitone from the blood in cases of poisoning is related to this finding - barbiturate is a weak acid and increases alkalinity [41]. Organic acids, anions and ions bound to proteins are removed by the active tubular secretion process. Different compounds compete with each other in this process. In the early days of penicillin, the half-life of penicillin in the body was increased by giving it as a suspension in oil or by providing another acidic drug such as probenecid as a compound. eliminate competition. The liver is in the most important place for detoxification because the blood goes to the liver after removing the toxic substances from the digestive system. Many biological changes occur in the liver and metabolites can be secreted into the stomach and small intestine for excretion. Diethylstilbosterol (DES) is 130-fold more toxic in rats ingesting the bile duct, suggesting that biliary secretion is the only way to eliminate DES. Compounds that can activate liver enzymes such as phenobarbitone increase biliary excretion of substances, as well as drugs such as spironolactone that can increase liver production and decrease. It is not considered a gas exchange, but it is an active part of the elimination process. Substances not absorbed from oral intake are excreted in the faeces. The best way to get rid of paraquat, a pesticide that can cause lung damage from accidental poisonings, is to bind it to a powder hose and dispose of it properly [42].

METABOLISM: It is clear that many evolutionary changes have evolved in humans. If a person is not exposed to environmental toxins, these enzymes may not be produced because there is no need for them. Excretion of toxic substances is one of the body's defense mechanisms, and (a) elimination of unchanged toxic substances through urine, faeces and other excretions, (b) biological transformation, transformation or structures, mainly the liver, to produce more water a solution for kidney failure, (c) structural changes for normal elimination and (d) host defense mechanisms such as immunity, tolerance, phagocytosis, etc. All metabolic reactions are enzymatic, and can be classified into hydrolysis, oxidation and reduction in the first stage, occurring in the soluble mitochondrial or microsomal compartments of the liver. In the next step, these biomolecules are combined with a polar or ionic component to increase their solubility in water [43]. There may be more than one metabolite in many of these reactions and many other metabolic processes as well as different pathways in a random biological system. When all these pathways fail due to the stress of the biological system on a toxic substance, there is only one person who fails [44].

Applied Areas of Toxicology

As mentioned earlier, the applications of toxicology are broadly divided into (a) chemical and legal toxicity, (b) economic toxicity including the toxicity of foods, drugs and pesticides, and (c) environmental toxicology, which includes Pollution studies, industrial and occupational health, divided.

Clinical And Forensic Toxicology

Clinical Toxicology

A clinical toxicologist works with people - his lab is a hospital; his test subjects are people who don't have access to testing. A clinical toxicologist deals with the effects of chemicals on the human system and is called upon to treat someone who has overdosed on a drug or pesticide to end their illness. His life also plays an important role in clinical trials conducted for new drugs. A large proportion of human deaths are caused by toxic substances: about 1.6 percent of all deaths among children under the age of five in the United States [45]. Investigating the adverse effects of medical professionals in large-scale human trials and participating in suicide and life-threatening cases involving toxic substances to bring victims back to life with appropriate procedures. Much of the information in clinical toxicology can be obtained from epidemiology, for example by collecting information on past victims. This is done in the USA through organized poison centers, which handle poisoning cases, document these cases and provide information for use by other centers[46]. These are stored on the computer and can be retrieved by users over the network. Drug interactions in the human body, involving more than one drug, are a problem facing the clinical toxicologist. The administration of barbiturates in epileptic patients increases the metabolism of diphenylhydanthone (anticonvulsant), so that the dose can be increased [47].

Barbiturates stimulate liver enzymes that metabolize hydant ions. Bleeding (breakage of blood vessels) is common in heart patients with thrombosis, discharged from the hospital and stabilized with anticoagulants. After home barbiturate therapy is discontinued, anticoagulant metabolism decreases and bleeding occurs. Another interesting example is protein binding to the 1021-membered albumin molecule, which is the most important defense mechanism of the biological system. It also contains protein and red blood cells to improve binding [48]. The binding part of the drug cannot produce an immediate effect, but not quickly. When two drugs compete for protein binding, many unexpected side effects occur, such as tolubutamide (antidiabetics) and sulfonamides (antibacterial). Both bind to proteins, but the sulfonamide can displace tolobutamide from protein binding sites. If these two drugs are given together to a person with diabetes, they may experience hypoglycaemia, or a drop in blood sugar to very dangerous levels.

Traditional treatment methods are improving and understanding the basic metabolism of the poison, cyanide poisoning is converted to nitrite to produce methemoglobinemia, which releases cyanide from cytochrome oxidase. Next, sodium thiosulfate converts the soluble cyanide into harmless sodium thiocyanate. Recent developments have improved methemoglobin-producing compounds such as dimethylaminophenone

and dimethylpropiophenone. Cobalt EDTA and vitamin B12 have been effective in treatment [49].

Forensic Toxicology

Although the clinical toxicologist works with the living person, and in case of intoxication, the toxicologist focuses on the deceased person, how he or she will recover, and uses the same methods as the clinical toxicologist to investigate the cause of the disease. It may be called an anesthesiologist for the disease (17). Diseases caused by illegal alcoholic beverages, often adulterated with methyl alcohol and other contaminants, are common in our country. Adulterated substances can also kill like the previous case (1986) of N of contaminated glycerin and ethylene glycol, which was the subject of the Justice Lentin Commission in Bombay. There are few other situations like this in the developed world, and it is very similar to a situation that happened in America more than 50 years ago in 1937[50]. 11 gallons and six pints of Elixir sulfanilamide and 72 % ethylene glycol solvent was distributed and increased. More than 100 deaths were due to nephrotoxicity or nephrotoxicity. The mechanism of ethylene glycol toxicity was investigated and determined to be due to deposition of calcium oxalate crystals in the kidneys and stone formation [51]. This phase led to stricter enforcement of food and drug laws, and such incidents are rare in these countries, due to high public demands for compensation. The trade in addictions and drugs such as cocaine, opium, morphine, heroin, marijuana, etc., is a big business in the world today, and there are many deaths caused by this drug activity. One of the main goals of human toxicology is to collect data on human toxicity that can identify specific chemical accidents and agents for the medical management of these cases [52].

Regulatory Toxicology

In developed countries, especially since 1970, many laws have been passed to protect people from real and imagined chemical attacks. The Federal Fungicide and Rodenticide Act, Toxic Substances Control Act, Safe Drinking Water Act, Clean Air Act, etc. in the United States and the regulatory bodies of the Environmental Protection Agency and the Food and Drug Administration have been very active more. In India we have such practices which are not practiced very much. An Environmental Protection Act was passed in 1986, but no regulatory body has yet been established (5). All these agreements require strong toxicologists to resolve violations and change and correct technical aspects. Legal institutions are empowered to deal with legal violations and to resolve scientific and technological issues [53]. But since most of these cases are metascientific, a non-scientific judge with the power of common sense can make the final decision in these cases.

Administrative laws are implemented in all countries after a crisis [54]. It is interesting to know that one or two deaths per day are caused by an accident such as a car accident as part of the accidents that we face. But if two people get sick from the same drug, it becomes a headline and creates new legal restrictions. When a law is passed, it always creates one or more public agencies, or expands an existing agency. So we get a new set of laws as a result of the original law by reading, making laws, doing, interpreting and administrative decisions to solve the problems that arise from the new set of laws. And then we get the rule of law not only by law, but by bureaucracy. These are words of wisdom from the US government's 1968 announcement on "The Environment Has Quality". This is exactly what is happening in our country 20 years later [55].

Food Toxicology

Food adulteration is intrusion, intrusion, or intentional adulteration for the greater good. In freshly cooked food, many impurities are destroyed by high heat. An interesting example is poisoning caused by eating uncooked cassava (tapioca) in Africa due to cyanogenic glycosides. In India people eat boiled cassava and there is no such problem. Processed food is more contaminated. Food fraud in our country is an art, and according to science, it cannot be said about mere fraud [56].

Environmental Toxicology

A healthy person should be comfortable with his environment twenty-four hours a day. A working man spends eight hours a day at work and the rest of the time at home and in his environment. The state of health of a person in relation to his work environment, called occupational hygiene, and the effort to maintain the workplace, called "industrial hygiene", go hand in hand. both things. Occupational health can be defined as the science and art dedicated to the assessment, evaluation and control of environmental conditions or stressors arising from the work environment, from or workplace that may cause illness, health and welfare problems or inconvenience. uncertainty among employees. If that definition extends to the environment outside the workplace and disease or illness among people in the community, it is called environmental health. Occupational health is related to workplace pollution while environmental health is related to environmental pollution [57]. The process is the same for both courses. Stress in the workplace can be caused by noise, heat, chemicals etc., but in the general environment it can be air, water and food pollution. In India, while environmental pollution is widely reported, workplace pollution is less reported. A toxicologist has many roles in these two studies, identifying the type, nature, amount and source of pollution, studying its effects on people, including the ways and means ways to reduce this pollution are all part of the work of a toxicologist [58].

Toxicology in Political Conflicts

One wonders what is so toxic about political conflicts, but both episodes show how long-distance communication can generate so much controversy, including research. toxicology and disease research. A large amount of scientific work and financial investments in these areas have provided useful scientific information - but in all ways it is not the same.

The TCDD Affair or the Agent Orange

Agent Orange is the code name for a chemical agent that was used for eight years in mass quantities by the US military during the 1962-1970 Vietnam War to deny food supplies to the white Viet Cong. destroying previous results. The substance "Orange" is equal parts 2,4,5-trichlorophenoxyacetic acid (2,4,5T) and 2,4-dichlorophenoxyacetic acid (2,4D). Both of these compounds are harmless to humans, but a small contaminant, tetrachloro-dibenzodioxin, or TCDD, is well known. TCDD is produced from trichlorophenol when burned, and manufacturers are allowed to use up to 2 ppm. But since the demand is greater than the supply, the quality control can be reduced for a short time. Saigon hospitals in the early 1970s reported birth defects in newborns caused by TCDD.

Many plants worldwide producing chlorophenols have been reported since 1949, mainly chloraquine, an occupational disease caused by exposure to TCDD. As the research and debate continued, a problem in the United States intensified. In 1971, a condo owner sprayed furnace oil in the attic to prevent dust in Times Beach, Missouri. It is a place of recreation and entertainment. Birds, cats and dogs began to die in this area. 43 of the 85 horses killed died during the year. 16,000 liters of trichlorophenol waste was found mixed with waste oil. The concentration of TCDD in oil was about 300 ppm and in soil 30 ppm. Finally, in 1982, the EPA purchased the entire beach to prevent human damage. The next problem was the explosion in 1976 at the ICMESA plant in Seveso, Italy, which resulted in 2.4.5 T. The nearby community of 37,000 people was exposed to various types of TCDD. The entire city was evacuated, the contamination cleared, and the people were allowed to return. About 184 cases of chloraquine were reported. However, no birth defects or deaths were reported in children born to exposed pregnant women. [59]

Toxicology of TCDD: TCDD is a total chemical. When scientists improved their methods and started looking for them, they found them all over the earth. The half-life in shallow soil is ten years. The sun and microorganisms destroy it. The guinea pig is the most sensitive species with an oral LD50 of 0.6 µg/kg body weight. Hamsters are very sensitive

with an oral LD50 of 1157 µg/kg. This is explained by the rapid growth rate in hamsters. TCDD has many reproductive effects such as oral cancer, kidney disease, stomach disease, and other rodents. It is also carcinogenic to mice and rats. Symptoms in people who are less sensitive to chloraquine include gastrointestinal disorders, effects on vital enzyme systems, and other mental disorders that may occur. Soft tissue sarcomas (a type of cancer) reported in Swedish woodworkers caused by TCDD were not confirmed by studies in Finland and the state of Washington, USA [60].

After-tale

American soldiers who fought in Vietnam were so outraged by the results of animal studies that they filed a class action lawsuit in 1979 against the chemical companies that made Agent Orange. And these companies, in turn, sue the US government for the misuse of pesticides. These investigations led to several epidemiological studies by various agencies. The Veterans Administration, the Center for Communicable Diseases, and the United States Air Force conducted separate studies aimed at assessing human harm from exposure to Agent Orange. All of these studies concluded that serum TCDD levels were higher in subjects who took Agent Orange than subjects who did not. But this is not related to any medical condition. The Air Force study, "Operation Ranch Hand" continued in 2002 with the NIOSH study to cover 85 years of work with TCDD. A fund of 200 million dollars has been set up to pay compensation. Regardless of the outcome, TCDD considers the cake to be the largest human-made collection worth billions of dollars. Undoubtedly, an unpopular program in an unpopular war gave us the science of toxicology [61].

The Yellow Rain

On September 13, 1981, then US Secretary of State Alexander M. Hague announced at a press conference in Berlin that the Soviet Union had used deadly chemical weapons in Laos, Cambodia and Afghanistan, and The US government has physical evidence. Depended on its use of the three mycotoxins and active fungal metabolites do not spread locally. Toxins called trichocenes are produced by Fusarium fungi. Sometimes these contaminate the grains and it is reported that it affects the skin, vomiting, diarrhea and stomach bleeding. Professor Marocha of the University of Minnesota identified these as trichotenes. Since these poisons are yellow droplets that land on trees and soil, they are called yellow rain. The main supports for confirming the attack of yellow rain among Laotian refugees are non-scientific factors and the US Army Chemical Research and Development Center based on scientific evidence. But large parts of the United States are suffering. The academic world did not take this evidence at face value. One of them, Professor Matthew Musselson from Harvard University, decided to take up the cross to find the truth. In January 1982, the British Chemical Defense Agency at Porton Downs found large amounts of pollen in yellow rain samples. These findings were confirmed by the Canadian Agricultural Laboratory in Ottawa. US military scientists could not explain the existence of poison in a chemical warfare agent [62].

Discrepancy [63]

Symptoms manifest in an otherwise healthy person shortly after the consumption of food or water. The symptoms tend to persist and rapidly worsen. If multiple people ingest the same contaminated food or drink, they often experience identical symptoms simultaneously. The presence of poison in the consumed food, vomit, or waste is one of the most conclusive signs of poisoning.

Ailments [64]

Sudden onset of abdominal pain, nausea, vomiting, diarrhea, or constipation. Pallor with pupillary constriction can appear suddenly, along with neurological symptoms like sudden running or disturbances in sleep patterns. Paralysis, particularly of the motor nerves in the feet, liver dysfunction, and jaundice are further indicators. Oliguria, accompanied by blood and protein in the urine, and persistent cyanosis are also warning signs. People exposed to chemicals, especially in occupational settings, may rapidly develop gastrointestinal or neurological conditions.

Hazardous

The word poison is defined differently by different people. As we all know, poison affects everything and causes harm and death. As mentioned earlier, almost anything can be toxic if consumed in large quantities. The basic idea of toxicology is this. The most important factor in determining your effect on a substance is how much you use it. There is no doubt that the statistics of the toxic potential of different substances vary. Aspirin is less toxic than cyanide, but too much aspirin can be fatal. We can determine the overall safety and risk of certain compounds based on their decomposition potential and how harmful they are [65].

In addition, individual sensitivity to many chemicals and toxins varies, depending on factors such as individual metabolic processes, genetic background, duration of use and underlying health problems. What makes one person sick, may be longer and less likely than another. Why is poison a deadly and effective tool for murder? A poison that can be used as a war weapon must be highly toxic in small enough doses to kill. It should be easy to hide (in food or water) [66]. If taken orally, the taste and smell should be carefully masked. It must produce a delayed and paradoxical symptom, or an underlying disease may appear. Finally, it should be easy to grasp and easy to handle. Poisons and drugs have a special place among killers. The type of the agent, the dose, the time of the agent's entry into the victim's body, the medicinal and medicinal properties of the agent, etc. In most cases, the disease is transient, so it can be fatal early. This poison continues. This simulation improves the clinical picture of the real disease. The above substances can be used openly and openly, sometimes by coercion or threats, but they can also be used lightly and stealthily, like adding to a favourite food, to or substituting poison for prescription medicine Disappears bad tastes and Odors when eating. add, especially if strong spices are used [67].

Carcinogens

No doubt the history of corrosion and poisoning goes back to ancient times. The mechanisms of poisoning and poisoning are known, although it is not easy to understand. Definitions can also be used to identify toxic substances. There is no doubt that many types of poisons have been used for murder, past and present. These include drugs, toxins derived from plants, animals and bacteria, as well as "alternative drugs" such as antifreeze [68]. It is difficult to control the use of contaminants and identify them because of the variability and common nature of many toxins such as salt and pesticides. For example, some poisons are more difficult to identify because they have no taste or smell. The many ways that chemicals can affect the human system, including suppressing specific diseases and illnesses, and the ways in which they interact, increase the risk of poisoning. Because of the nature of intoxication, unlike other types of murder, the crime may not be detected. However, these problems can be reduced by considering the nature of poisons and their characteristics, mode of action, lethal doses and treatment methods for poisoning. Knowing the differences between acute and chronic poisoning can help us understand the needs of those who become ill[69].

According to the trends, more drugs are found in poisons such as cyanide and arsenic than in previous centuries. Willingness to commit crime and hatred are two different things. Persuasion refers to the reason or reasons behind the offender's desire to poison, which may be related to behavioral needs unknown to the offender. The obligation to perform an action is given as an intention. There are many ways to find evidence of intent, but the best place to start is for the investigating officer to remain neutral and refrain from making unwarranted conclusions when speaking to bystanders. search and search. Proving that the defendant knew in advance that the substance was deadly is one way to prove intent. Sometimes the audience shows this evidence and remembers the killer's bad words [70]. They may be found in poisoned books downloaded or

viewed by the criminal on the Internet. When a person secretly receives poison, the suspect suddenly reveals his identity or tries to hide his identity, giving criminal expertise. By determining the cause of the poisoning, investigators can determine how many victims the person poisoned and where evidence of those crimes may be found.

Knowing the motivation behind a criminal's behavior can help the police develop investigative strategies and guide the search for relevant evidence. Officials can refer to this information when deciding how to present a dispute in court. Researchers should be cautious when drawing conclusions about enthusiasm. Even if the cause of a disease is clear, it is necessary to examine it again to find out the true cause or causes that caused it in the first place. Law enforcement should be cautious when a suspect gives an explanation of his motive because it may be an attempt to divert attention from the ongoing investigation [71].

Legal Toxicology

The field of toxicology deals with the detection and measurement of drugs and other biodegradable or toxic substances in body fluids such as blood. The method of qualitative evaluation tests indicates two possible results: positive, indicating a drug or poison, or negative, indicating the absence of a drug or poison. These tests are known to measure when the concentration of a drug or toxin is detected [72]. There are two distinct approaches to the criminal applicability of the results: a preliminary investigation and a (quantitative) test. Some toxicology laboratories perform drug classification. The application of many scientific methods in the criminal justice system is known as forensic science. This could lead to civil lawsuits or legal action. A branch of toxicology known as toxicology applies the concepts of toxicology to legal purposes. Autopsy toxicology, work-related toxicology, and drug testing are the three subcategories. In the past, morgue examinations were the only cases handled by toxicologists with disease expertise. Currently, they handle many cases. A court of law must be able to scrutinize the toxicologist's work and opinions (9). It is possible to present reports and conclusions as proof, and the doctor of toxicology is frequently called upon to give testimony.

A toxicologist working in toxicology must consider the investigation, including possible clues, evidence found at the crime scene, and background information in the case. A toxicologist uses this information, along with diagnostic measurements, to identify the toxic substances involved in an incident and their concentration levels. He must determine the potential importance of the substance or substances in the case [73]. Applications of toxicology and research to resolve legal disputes are called legal toxicology. This program is often related to work in the criminal, judicial, police and investigative fields. Although these relate to the civil rather than the criminal justice system, other aspects of toxicology include the investigation and identification of drugs, as well as compliance with the law. agriculture, manufacturing and health regulations (to create clean air, clean water, and goods). Like psychologists in criminal cases, analysts working in these public areas may find that their work draws media attention to court cases. And let the other side understand the advantages and disadvantages of each other's methods. They are usually managed by hospital biologists or clinical toxicologists who work with emergency poison centers[74].

A small percentage of these cases are referred to a toxicologist because of a request for investigation of a lawsuit or suspected poisoning. The detection and understanding of toxins, their physiological effects on humans and animals, and the development of countermeasures are areas of concern for toxicologists. The amount and type of toxic incentives offered by criminal investigation agencies varies widely, but most offer some. However, many hospitals, medical examiners, health-related investigators, and criminal justice research institutions continue to encourage toxicity. Police officers can be dispatched to nearby businesses by lab staff (5). The misuse of illegal substances has become a global issue affecting all aspects of society, making the work of the toxicologist extremely important. Drugs and toxins are found in body fluids, tissues and organs and can be detected by toxicologists. In addition to legal requirements such as crime labs and medical research offices, medical center laboratories-where the ability to detect the weight of drugs can mean the difference between life and death. Disease-other health facilities are responsible for drugs and more. It's a weakness. Drug users should also use their services. Early examples include testing young people who participate in lead painting with blood samples or examining urine samples from drug addicts participating in methadone maintenance programs [75]. Checking

Diagnostic laboratories use a variety of analytical methods, but most combine chromatographic and immunoassay methods to identify and quantify drugs and toxic substances. Gas chromatography is often used in laboratories for the analysis of alcoholic beverages. As a preliminary test or evaluation, enzymes and color schemes are used. Spectrophotometric differences between deoxygenated hemoglobin, meta-hemoglobin and carbohydrates of hemoglobin can be used to test for carbon monoxide in the environment. Gas chromatography, diffusion, and colorimetric methods are other methods for carbon monoxide analysis [76]. Colorimetric and analytical measurements are two methods of testing for cyanide. Blood and urine samples can be screened for many drugs and drug classes using an immunoassay test. The immunoassay test is used to identify substances such as cocaine metabolites, benzodiazepines, amphetamines, medicinal substances such as thistle and opioids. For the qualitative and statistical evaluation of samples related to harmful substances, chromatographic processes such as thin layer chromatography (TLC), gas chromatography (GC), high-performance liquid chromatography (HPLC) and coupled chromatography and mass spectrometry methods (GC/ MS, GC/MS/MS, LC/MS, LC/MS/MS) are used [77]. Atomic absorption spectrophotometry can be used to analyze samples of arsenic, mercury, cadmium, lead and other heavy metals for metal poisoning.

The methods used to evaluate substances must be validated to ensure the correctness, accuracy and applicability of the method in order for the results of toxicological tests to be valid. Determining lower and upper extraction limits as well as search limits are part of the process. The identification testing method evaluates the import of previous tests and samples to identify harmful substances [78]. A toxicologist working in predictive science must be able to evaluate process efficiency and understand the importance of validation. Medico-legal aspects in criminal and civil cases should be assisted by the results obtained by proper scientific methods [79].

Conclusion:

During an investigation, forensic scientists collect, preserve, and evaluate scientific evidence. While some forensic experts visit to gather evidence, others take a scientific approach and analyse cases brought to them by others. Forensic examiners are experts in both criminal and civil trials, and can represent the prosecution or the defence in addition to the trial. Although all fields are considered international science, most of the issues related to law enforcement are now covered by specialized agencies that have grown over time.

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Consent for publication

Nil

Authors' contributions

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