Methodology of Toxicometric Evaluation of Acute Poisonings

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Abstract: This article introduces a novel methodological framework for evaluating acute chemical illness, facilitating the identification of the primary impact of toxic agents on homeostasis. This approach enables tailored detoxification strategies and supports a rigorously justified forensic medical evaluation of the severity of chemical injuries and their postmortem diagnosis. By offering insights into the direction of toxic agent effects, this methodology contributes to more effective management of chemical trauma cases. It enhances our ability to provide targeted medical interventions and ensures a comprehensive understanding of the pathological processes involved, thereby advancing forensic medicine practices in this domain.

1 INTRODUCTION

Chemical pollution poses a significant threat to human life and the environment globally, including in Uzbekistan, driven by extensive chemical production, international trade, and widespread use in various sectors. With over 7 million chemical substances synthesized and approximately 70 thousand in daily use, the potential consequences of this pollution are vast and unpredictable. Public health protection from chemical pollution receives insufficient attention in environmental programs, despite humans being both perpetrators and primary victims of environmental disasters. Biomonitoring for acute human poisoning could provide valuable insights into environmental conditions, yet the country lacks adequate measures and interdepartmental coordination for prevention. Responsibility for chemical product safety falls on the Ministry of Health's sanitary and epidemiological service, primarily focused on setting maximum allowable concentrations (MACs) and production control. However, during emergencies, human exposure often far exceeds MACs, necessitating the development of acute toxicity passports. This study aims to devise a new methodological approach for assessing acute poisonings, leveraging real clinical and morphological data from forensic medicine centres.

2 MATERIALS & METHODS

The material for the research consisted of 252 cases of acute poisonings with the most common industrial, household toxins, and medications. The study employed multidimensional statistical analysis methods: factor, cluster, nonlinear regression analyses, and a probit graph of the "poison concentration-effect" relationship.

3 RESULTS & DISCUSSION

Below is the methodological rationale and examples of toxicometric assessment of industrial, household, and medicinal products. The use of toxicometric (quantitative) assessment of chemical illness in forensic medicine is proposed for the first time by the author of this investigation.

In the first section, "Passports for the acute toxicity of a chemical compound," an assessment of the risk of death for victims is provided across the

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entire range of recorded concentrations of toxins in the blood. For this purpose, the "probit analysis" method is used (Fig. 1).

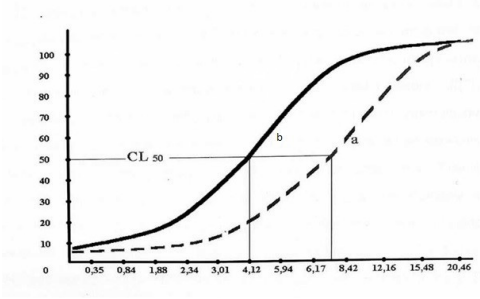


Figure 1. Probit graph of the "free hemoglobin concentration-effect" relationship in acute poisonings with acetic acid. On the abscissa axis - the logarithm of intravascular hemolysis level, on the ordinate axis - the percentage of the risk of death.

In a typical case, the probit plot of the "concentration of poison-effect" relationship has an S-shaped form. The lower flat portion of the graph (or its lower asymptote) corresponds to poison concentrations where the initial magnitude of chemical injury does not exceed the limits of the physiological defense of the organism, and the outcome of poisoning is always favorable. This level is denoted as CL0 - the maximum tolerable concentration of poison. It is characterized by the onset of acute clinical symptoms of poisoning and can be labeled as the threshold for acute poisoning.

The next ascending portion of the graphical curve corresponds to concentrations where the outcome of poisoning is uncertain, and the risk of death exponentially increases with the rise in poison content in the blood. Within these concentrations, the organism is in a critical state, and the treatment outcome largely depends on the organization of intensive detoxification therapy. When assessing the critical condition of the organism, the mean lethal concentration of poison in the blood (CL50) can be used as an objective criterion. From a forensic perspective, this level of poison in the blood is considered life-threatening, and the data from poisoning are regarded as severe bodily injuries (harm to health) dangerous to life.

Having reached a certain limit, and regardless of further increases in the concentration of the toxic agent, the probit plot curve returns to a horizontal position. This segment (upper asymptote) corresponds to CL100 - the absolutely lethal concentration of poison or a life-incompatible chemical injury.

Thus, the analysis of the "concentration of poison-effect" relationship is a valuable tool in studying the quantitative aspects of the relationship between the absorbed dose of a chemical substance and the nature of the overall response of the organism. From the perspective of this relationship, the crisis of homeostasis should be characterized as an unstable, transitional state between the two only possible polar outcomes of poisoning - recovery and death.

Using such normative graphs, an objective prognosis of the outcome can be provided even at the very beginning of a chemical injury. In accordance with the risk of death, priority service can be ensured for the most severely affected contingent in mass chemical disasters. The results of the toxicometric assessment of the risk of death in acute poisonings with industrial, household poisons, and pharmaceuticals are presented in Table 1.

Table 1. Results of toxicometric assessment of mortality risk in acute poisonings with industrial, household toxins, and medicinal preparations.

Name of Poison	Toxicometric Parameters				
	Ch0	Ch25	Ch50	Ch75	Ch100
1	2	3	4	5	6
Dichloroethane (μg/kg)	2,76	8,31	14,63	19,20	26,44
Carbofos (μg/kg)	0,3	176	1,04	1,92	3,03
Chlorophos (μg/kg	0,21	1,22	3,81	6,41	8,51
Acetic Acid (free hemoglobin in blood plasma, μg/kg)	1,48	5,62	10,84	16,80	33,88
Phenobarbital (μg/kg)	16,0	38,15	66,69	151,34	215,72

Critical condition is not only a specific form of disturbances in the body's vital functions but also a distinct phase in the course of a pathological process. Unfortunately, in the majority of contemporary studies, the dynamics of mortality risk in poisonings are not considered. However, this indicator is no less important as a criterion for the danger of a chemical compound than the poison level in the blood. Figure 2 presents graphs of survival probabilities for patients

at each moment in time during adverse outcomes of various chemical diseases (Fig. 2).

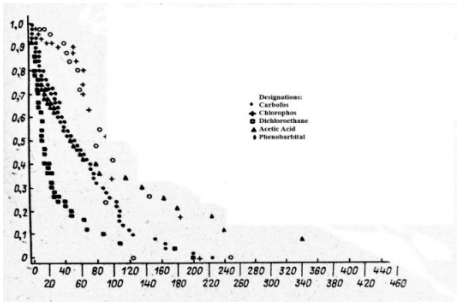


Figure 2. Duration of life for victims in adverse outcomes of acute poisonings. On the ordinate axis - the probability of survival at time T; on the abscissa axis - time (hours). This indicator is obtained using a computer when determining the reliability function in a special mathematical model by D.R. Cox.

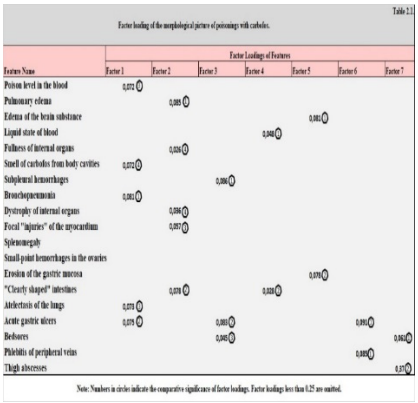
Upon scrutinizing the graphs, it's evident that the survival likelihood declines rapidly within the initial hours of dichloroethane poisonings, whereas with acetic acid or carbofos, homeostasis reliability diminishes less drastically, allowing the dying process to extend up to 120-200 hours.

Conversely, irreversible effects in phenobarbital poisoning manifest relatively late, typically after severe pulmonary complications set in, such as pneumonia. Thus, based on mortality intensity, dichloroethane merits classification as an extremely hazardous substance, while carbofos and acetic acid qualify as highly toxic, and phenobarbital as moderately toxic poisons. This classification becomes pivotal for patient triage during mass poisonings.

In the study of acute poisonings, discerning between the direct impact of the poison and the body's response poses a crucial challenge. The specificity of subsequent clinical symptoms and morphological changes remains largely unexplored, impeding informed pathogenetic treatment and expert assessment of illness severity and postmortem diagnosis.

To address this complexity, factor analysis emerges as a methodologically sound approach, enabling the identification of interdependent features and their correlation with the overall reaction of the organism.

By delineating the significance of each feature within the studied process, factor analysis provides invaluable insights into the pathological mechanisms underlying acute poisonings, exemplified by the clinical-morphological profile of organophosphorus compound poisoning.Table 2. Factor structure of the clinical and morphological picture of poisonings with carbofos.



Factor loading of the morphological picture of poisonings with carbofos.

Feature Name	Factor Loadings of Features						
	Factor 1	Factor 2	Factor 3	Factor 4	Factor 5	Factor 6	Factor 7
Poison level in the blood	0,972						
Pulmonary edema		0,885					
Edema of the brain substance					0,883		
Liquid state of blood				0,948			
Fullness of internal organs		0,836					
Smell of carbofos from body cavities	0,972						
Subpleural hemorrhages			0,886				
Bronchopneumonia	0,883						
Dystrophy of internal organs		0,836					
Focal "injuries" of the myocardium		0,937					
Splenomegaly							
Small-point hemorrhages in the ovaries							
Erosion of the gastric mucosa					0,979		
"Clearly shaped" intestines		0,979		0,838			
Atelectasis of the lungs	0,973						
Acute gastric ulcers	0,979		0,883			0,893	
Bedsores			0,985				0,964
Phlebitis of peripheral veins						0,882	
Thigh abscesses							0,97

Note: Numbers in circles indicate the comparative significance of factor loadings. Factor loadings less than 0.25 are omitted.

It is known that chemical substances affect the cells of tissues and organs only when their concentration exceeds a threshold. Thus, if clinical and morphological signs of poisonings are arranged according to the magnitude of their concentration thresholds (as depicted in Fig. 3, using acetic acid poisoning as an example), they will be grouped based on the resistance of each tissue to the specific toxic substance.

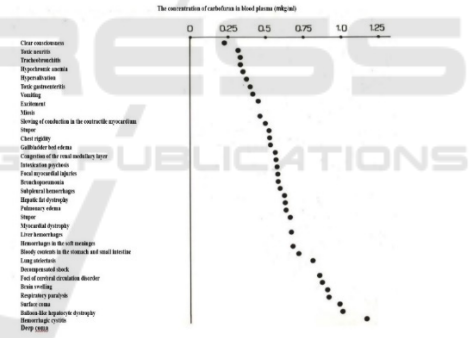


Figure 3. Concentration thresholds for the main clinical and morphological signs of poisonings with the mentioned toxic substance.

As indicated in the presented table, the critical phase of chemical poisoning is characterized by the greatest clinical diversity. Its distinctive feature is the involvement in the pathological process of tissues, organs, and systems to which the selective action of the poison does not directly extend. With the help of this program, it is possible to establish a typical clinical-morphological picture of poisonings for any specific magnitude of chemical trauma based on the degree of hemoglobinemia. Conversely, based on the nature of clinical and morphological changes, one can deduce the highest concentration of the toxic substance.

Ultimately, the outcome of acute poisonings depends on whether the body can eliminate the absorbed dose of the poison. Therefore, in our comprehensive problem, special attention is paid to studying the kinetics of poisons in the blood. For each type of chemical substance, we have developed normative toxicokinetic graphs using a computer program we created. Leading parameters of this process have been determined: the elimination rate constant and the half-life period of the poison in the blood. These parameters should be considered fundamental in monitoring the resuscitation period of acute poisonings, allowing forensic experts to assess the correctness of the treatments administered (Table 3).

Table 3 Comparative Characteristics of the Toxicokinetics of Organophosphorus Insecticides

Name of the Poison	n	Initial level of poison in the blood (μg/kg)	Elimination rate constant of the poison (Ke)		
	Half-life of the poison in the blood (T1/2)				
	Maximum duration of the toxicogenic phase (hours)				
Carbofos	150	0,15±0,06	35	19,80	72
Chlorophos	100	1,70±0,25	39	17,76	53
Foxim	107	0,87±0,05	37	18,75	66
THM-3	69	1,02±0,15	23	30,13	98
Metafos	50	0,96±0,12	43	16,11	50

It is always advisable to study the course of chemical illness from two perspectives: what the poison does to the organism and how the organism itself affects the biotransformation of the poison. Our research results have shown that toxic coma, exotic shock, and several other critical states of the organism can significantly prolong the duration of poison circulation in the blood. This circumstance needs be taken into account by forensic experts when organs are removed from corpses for forensic-chemical examinations.

The body's response to its damage is not an instantaneous reaction but a process unfolding over time through specific phases of interacting factors. In chemical illness, where the sequence of toxic effects is, to a certain extent, a consequence of the distribution and biotransformation of poisons in the organism, the analysis of this process is particularly relevant. Figure 4 presents the toxicodynamics of the clinical and morphological manifestations of acute poisonings with chlorophos and carbofos.

The pathogenetic connection that effectively exists between different types of toxic effects is expressed in their sequence. From the perspective of the dynamics of poisoning, each preceding stage of chemical illness prepares and shapes the subsequent one. Therefore, as a risk factor for bronchopneumonia in this poisoning, all preceding toxic effects and syndromes, especially bronchorrhea, chest rigidity, and artificial ventilation of the lungs (AVL), should be considered.

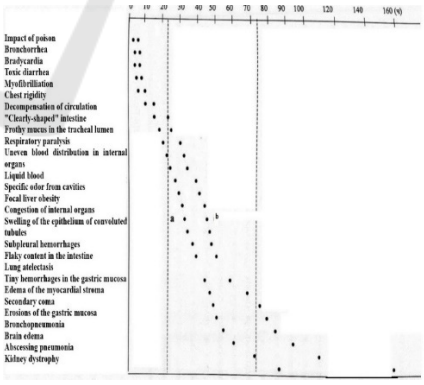


Figure 4. Toxicodynamics of the clinical and morphological picture of poisonings with carbofos and chlorophos.

Before our research in clinical and forensic toxicology, the study of critical conditions in poisonings was typically fragmented. For the first time, we proposed the use of multidimensional statistical analysis in synthesizing the entire complex of chemical illness (Fig. 5).

Figure 5. Structural portrait of acute phenobarbital poisoning.

This figure demonstrates the structural portrait of acute poisonings with phenobarbital obtained through the cluster analysis method. This picture is presented as a graph, where the vertices represent clinical-morphological and laboratory-functional features of chemical illness, and the connecting edges reflect the direction and inter-system connections. In addition, the arrangement of features is ranked according to their influence (level of proximity) on the outcome of the illness. In other words, the upper part of the graph contains features that dominate in the mechanism of thanatogenesis (respiratory paralysis, pneumonia, etc.), while the lower part of the graph concentrates indicators that do not have a significant impact on the outcome of poisoning.

4 CONCLUSION

The implementation of toxicometric assessment in acute chemical illness offers valuable insights into the primary effects of toxic substances on homeostasis, facilitating tailored resuscitation interventions and scientifically informed expert evaluations of illness severity and post-mortem diagnoses. However, addressing the complexities of medical care in acute poisonings, particularly during mass disasters, necessitates innovative solutions such as intelligent computer systems. The sheer volume and diversity of chemical illnesses make comprehensive physician training in pathogenesis, clinical manifestations, and treatment virtually unattainable. Consequently, the development and deployment of such computer-based programs are imperative for enhancing medical response capabilities. Moving forward, collaboration with institutions like the Research Institute of Clinical and Experimental Lethal would be vital for advancing research and implementing practical solutions to improve outcomes in cases of acute chemical poisoning.

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