Development Of Predictive Toxicity Measures For Assessing Risks From Catastrophic Chemical Releases

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Abstract

The Chemical Security and Analysis Center (CSAC), a U.S. Department of Homeland Security component, is responsible for homeland security needs related to chemical threat awareness. The CSAC has been charged to determine public health impacts (injuries and deaths) potentially associated with catastrophic chemical releases. The following methodology was developed to address this need, and applied to 17 chemicals to date. Injury-severity categories were defined based on expected duration, permanency and extent of potential injuries for acute exposures. These categories include 'mild injuries,' 'incapacitating injuries,' 'life-threatening injuries,' and 'death.' As described below, probit curves were developed for each chemical, exposure route (inhalation, ingestion, dermal contact), and injury-severity category. First, toxicity endpoints were defined for each exposure route and injury-severity category through a literature review. Next, dose-response (esp. incidence) data from key studies were evaluated, and allometric equations were used when necessary to derive human-equivalent exposure estimates from the results of animal studies. Median effective and lethal exposures were calculated for each exposure route and injury-severity category based on probit analyses of the transformed data. Alternative methods were developed to derive predictive toxicity measures when the data from empirical investigations were inadequate (e.g., route-to-route, severity-category-to-severity-category, and chemical-to-chemical extrapolations). In addition, methods were developed to assign uncertainty factors to each predictive measure, enabling the depiction of a bounding range that reflects the uncertainty associated with each measure. The resultant predictive measures serve as toxicological inputs to the CSAC's Chemical Terrorism Risk Assessment, and represent a more refined way to assess and incorporate non-lethal effects into other risk assessments.

Problem

Predicting the impacts of catastrophic chemical releases requires estimating acute exposure concentrations or doses causing toxic effects across a wide spectrum of severity, ranging from mild injury to death. Few chemicals of concern have comprehensive data sets on which to base predictions for the accidental and intentional release scenarios envisioned.

Approach:

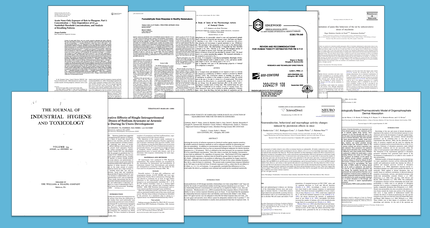
1. Define injury severity categories
2. Develop protocol for deriving predictive toxicity measures
3. Conduct literature search and data evaluation
4. Develop predictive toxicity measures
5. Denote uncertainty

Injury severity categories:

- Mild
  - Minor discomfort, not disabling, short-term, reversible effects, such as local irritation, nausea, mild narcosis or mild allergic symptoms; may seek or be provided medical attention, though should not require inpatient care.
- Incapacitating
  - Serious effects, causing performance degradation, but not life-threatening or progressive; may require medical attention; Likely admission for observation or care.
- Life-Threatening
  - Direct threat to life without emergency medical treatment; e.g., includes anaphylactic reactions.
- Lethal
  - Irreversible progression of effects leading to death; not amenable to medical treatment.

Protocol Highlights

- Predictive toxicity measures are sought, to represent the central tendency of general population's response to acute exposures (i.e., ≤4 hours).
- Collect & organize toxicology data
  - Reports are categorized and sorted based on key parameters
  - Resources include studies serving as the basis for acute exposure guidelines and regulations
- Identify relevant toxic effect endpoints for each injury severity category and exposure route
  - Use data from all or only one toxic endpoint?
  - Which endpoint is most pertinent?
  - Gradations of a single endpoint represent a single or multiple injury severity categories?
- Professional judgment: identify relevant toxic effect endpoints, consider health effects that develop during exposure or ≤ 14 days post-exposure
- Select the most appropriate data
  - Data from multiple studies may be used if a single study does not demonstrate a dose-response relationship
- Calculating predictive toxicity measures
  - Animal data may be extrapolated to humans using allometric equations to address systemic effects
  - Exposure/population-response probit plots are developed from human equivalent doses using binary or ordinal logistic regression
- Additional steps are taken to address limited or missing information, e.g., severity-to-severity category, route-to-route, and chemical-to-chemical extrapolations
- Uncertainty is denoted using guidelines



Guidelines for Selecting Best Available Study
Study
Reports incidences (or means with SEs or SDs)
Previously vetted and used to set AEGLs
Peer-reviewed or followed GLPs (or grey literature)
Test Species
Human subjects (clinical or epidemiological data)
Animal species relevant and appropriate for extrapolating to humans
Design
Appropriate control groups
Adequate number of exposed groups (≥ 3 groups)
Adequate number of test subjects per group
Exposure
Appropriate exposure route (inhalation, ingestion, or dermal contact)
Well-characterized exposures (appropriately spaced and quantified)
Exposure duration 4 hours (or ≤ 24 hours; ≤ 48 hours for dermal contact)
Adequate post-exposure observation period (onset, reversibility)
Findings
Demonstrated dose-response relationships
Treatment-related measurements statistically different from controls
Consistent with other studies

Source of Uncertainty	Guideline	Contribution to Uncertainty
Chemical-to-Chemical Extrapolation	No chemical-to-chemical extrapolation is required	▲
	Chemicals share common biochemical mechanism/target of action and have similar lipid and water solubility	▲▲
	Chemicals have similar, instead of common, biochemical mechanisms/targets of action (e.g., both inhibit the citric acid cycle, by do so by inactivating different enzymes) and have similar lipid and water solubility	▲▲▲
	Chemicals have similar biochemical mechanisms/targets of action, but dissimilar lipid and water solubility	▲▲▲▲
Route-to-Route Extrapolation	No route-to-route extrapolation needed, or extrapolating between injection (e.g., i.v., i.p., s.c.) and inhalation	▲
	Extrapolation required between injection/inhalation and ingestion routes	▲▲
	Extrapolation required between ingestion and dermal exposure	▲▲▲
	Extrapolation required between injection/inhalation and dermal exposure	▲▲▲▲
Injury-Severity Category to Injury-Severity Category Extrapolation	No extrapolation from another injury severity category is required	▲
	Extrapolation is required between adjacent injury severity categories	▲▲
	Extrapolation is required between mild and life-threatening injury or incapacitation and lethal injury	▲▲▲
	Extrapolation is required between mild and lethal injury categories	▲▲▲▲
Animal-to-Human Extrapolation	No animal-to-human extrapolation is required	▲
	Extrapolation is required from animal incidence data	▲▲
	Extrapolation is required from animal data, but without the benefit of incidence data (e.g., from an EC_{50} only)	▲▲▲
Inter-Individual Variability	Data from relatively homogenous study population extrapolated to general human population	▲
Database Uncertainty	Extensive database that includes clear evidence of causality (from animal or human studies), supplemented by metabolism, pharmacokinetic, and mechanism studies	▲
	Database that includes clear evidence of causality (from animal or human studies)	▲▲
	Limited database	▲▲▲

Results: Median Doses

	Inhalation (mg·min/m³)				Ingestion (mg/kg)				Dermal (mg/m²)			
	Mild	Incap	Life Threat	Lethal	Mild	Incap	Life Threat	Lethal	Mild	Incap	Life Threat	Lethal
Acrylonitrile	20,204	47,886	81,543	132,274	2.4	5.8	9.9	16	461	1,093	1,860	3,018
Arsenic Trioxide	3,376	11,479	54,020	58,071	0.72	2.5	3.0	3.4	---[1]	---	---	---
Brodifacoum	151	183	203	373	0.023	0.028	0.031	0.061	16	20	22	43
Fentanyl	1	8	70	11,666	0.0004	0.003	0.03	5.0	0.1	1	8.4	1,400
Formaldehyde	371	790	5,286	14,531	2.1	4.4	29	80	340	725	4,852	13,338
Hydrazine	33	23,800	46,666	121,333	0.002	1.5	3.0	7.9	1.4	906	1,779	4,620
Hydrogen Sulfide	33	50,490	60,748	77,284	---	---	---	---	33[2]	50,490[2]	60,748[2]	77,284[2]
Parathion	1,388	5,092	5,449	5,806	0.4	1.2	1.5	1.8	59	161	204	247
Phosgene	246	481	768	1,500	---	---	---	---	---	---	---	---
Picrotoxin	217	898	952	1,462	0.05	0.19	0.20	0.31	6.5	27	29	44
Potassium Cyanide	9,384	20,433	26,655	62,194	0.13	0.27	0.36	0.84	137	298	391	908
Sarin	1.7	105	125	175	0.00082	0.049	0.058	0.082	27	1,696	2,000	3,400
Sodium Fluoroacetate	1,913	3,360	5,880	16,333	0.41	0.72	1.26	3.50	1,731	3,043	5,347	14,852
Strychnine	569	591	612	2,599	0.12	0.13	0.13	0.56	---	---	---	---
Sulfur Mustard	25	75	2,020	4,932	0.0035	0.011	0.29	0.70	50[2]	500[2]	4,652[2]	10,000[2]
TETS[3]	69	287	304	467	0.02	0.06	0.07	0.1	2.1	8.6	9.2	14
Thallium Sulfate	2,920	4,694	7,547	12,133	0.6	1.0	1.6	2.6	---	---	---	---

[1] Not Estimated [2] mg·min/m³ [3] Tetramethylenedisulfotetramine

Low Uncertainty | Moderate Uncertainty | High Uncertainty

Conclusions

The protocol developed and described above enables derivation of predictive toxicity measures for multiple exposure routes and injury severity categories based on acute toxicity data that is typically limited for the chemicals of concern. These estimates, in turn, provide the basis for estimating the number of casualties (injuries and death) that may result from an accidental or intentional chemical release in the general population. The results can be used to inform decisions about medical facility requirements, development of triage and injury mitigation strategies, and prioritization of research and development efforts for reducing uncertainties.