When serious harm first appears in human trials

Why promising animal results cannot establish that an experimental peptide is safe

Plain-language research report | Sources checked 17 November 2026

What this review found

Some experimental treatments caused severe or fatal harm during phase I trials, after substantial laboratory and animal research. The reasons differed. Sometimes an animal lacked the human feature that made treatment dangerous. Sometimes there were already warning signs that did not prevent the human outcome. A few reassuring observations could not settle the question.

The best documented cases include antibodies, a small-molecule drug, an RNA treatment and engineered immune cells. These are different kinds of treatment. There is also direct evidence of severe reactions in a phase I trial of a short peptide. Those distinctions matter when applying the lessons to peptides sold for injury recovery or other uses.

What happened in people

TGN1412: six healthy recipients became critically ill. This antibody caused dangerous inflammation within hours in all six people given the active drug. All survived. Follow-up experiments found that an important group of human immune cells carried the drug's target, while the corresponding monkey cells did not. The way the antibody was presented in laboratory tests also affected whether the hazard appeared. [1–3]

BIA 10-2474: one participant died in a repeat-dose group. Five of six active recipients in the highest repeated-dose cohort developed serious neurological problems. The animal programme had contained neurological findings, so it would be wrong to say that every animal test was harmless. Later experiments found unintended molecular actions, but the exact cause of the human injuries remains unresolved. [4–6]

TAS266: severe liver-test abnormalities stopped the study. Three of four cancer patients developed major liver-enzyme elevations; these improved after stopping treatment. Animal tumour-killing experiments and selected cell tests had not established safe action in the human liver. The experimental report also recognized limits in rodent models and possible harmful antibody interactions. These events were reversible toxicity, not fatal liver failure. [7,8]

MRX34: four treatment-related deaths occurred during phase I development. The report concerned 85 cancer patients receiving a particular dosing schedule. Animal studies, including studies in primates, had not predicted the human pattern of immune-associated toxicity. The reactions that ended the trial occurred in expansion cohorts, showing that safety questions remain after the earliest participants have been treated. [9,10]

Engineered MAGE-A3 T cells: the treatment attacked the heart. The first two patients across two early protocols died from cardiac toxicity. Investigators found that the engineered immune cells also recognized a piece of the human muscle protein titin. The equivalent mouse sequence did not trigger the same response. The treatment was engineered cells, rather than a peptide injection, but it shows how an unintended biological recognition can matter. [11,12]

A directly relevant peptide example

LTX-315 is a short peptide injected into tumours as an experimental cancer treatment. In a phase I trial, four of 39 patients had grade 3 hypersensitivity or anaphylaxis. The authors still considered its safety acceptable in the studied cancer setting. The severe reactions remain important observations. [13]

Earlier mouse research showed tumour destruction and protective immune responses. That does not establish that the animal safety studies failed to predict the human reactions: the necessary matched safety comparison is not demonstrated in these reports. [14] The sound conclusion is narrower—short peptides can cause severe reactions, and a benefit in animals does not answer every question about safety in people.

What this means before using an experimental peptide

The word “peptide” describes a type of molecule. It does not tell you how strongly that molecule acts, which other targets it may affect, or how a person's immune system will respond. A safe use for one peptide cannot establish the safety of a different sequence, formulation, route or exposure schedule.

These cases do not mean that a particular peptide will cause the same harms. They show why an absence of reported problems in animals, or in a handful of people, is limited reassurance. They also cannot give a percentage risk for an untested product: the examples were selected because serious events happened.

Proper clinical development connects a defined product with carefully chosen exposures, monitoring, stopping rules and follow-up. Phase I helps discover how a treatment behaves in people; later trials are still needed to establish benefits and characterize further risks. [15] Using a peptide before that work is done means accepting unresolved questions about both benefit and harm, often without the monitoring and response arrangements of a trial.

Sources

These are original clinical or experimental reports, apart from the final regulatory guideline. The academic version explains the evidence and access limits in more detail.

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