Opinion

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The importance of identifying mode of action key events in occupational and epidemiological studies

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Key events are considered main elements when studying a chemical mode of action. In any chemical mode of action, key events are the biological, physiological, and biochemical changes that lead to an adverse health outcome. Thus, key events are crucial in describing a toxicological pathway and in understanding the development of adverse effects. These precursors of biological events are turning points toward the intuition, development and occurrence of a disease. The occurrence of these biological key events in the body is similar to tying knots in a rope. The similarity is that these knots occur in sequence, they strengthen each other, each knot cannot be undone once formed, and the beginning of the rope is connected to the end through these knots. Without the identification of key events, the mode of action cannot be described and the real threat of a chemical will not be completely understood. To develop a dose-response relationship in humans, a dose administrated in animals is usually extrapolated to humans through the multiplication of the dose many folds to assess similar dose effects in humans. This extrapolation from animals to humans has been always a problem because of the biological, physiological, and anatomical differences presented between the two species. Nonetheless, there have been always great efforts to get a standardized method to evaluate chemicals' toxicological effects in humans based on an explanation that is biologically reasonable. Since the toxicological data is usually more available in animals than in humans, toxicological effects evaluation in humans is mainly based on animal experimental results. On the other hand, occupational and environmental exposure studies are great resources to study humans' response to a toxicological chemical exposure, but most of these studies focus on exposure doses, frequency, and duration, and relate the exposures to any noticed adverse health outcomes. This is a great addition to the toxicological data and body of knowledge available, yet, it doesn't provide a deep understanding about the chemical internal behavior in the body, chemicals' kinetics or dynamics, or short and long term health effects. Not to forget that without the effort to identify or examine pre-identified key events in these human studies, the bulk of animal experimental data available for that chemical will be mostly useless in the sake of assessing risk in humans.

There is no doubt that identifying these key events or even testing them in the course of conducting occupational or epidemiological studies is a daunting task, which might seem impossible sometimes. However, there are weak or almost no efforts taken to develop tools to test key events in human studies, maybe because of the difficulty of the work, time limits, or sources available. However, the main issue stands within the concept of key events identification in human occupational or epidemiological studies. There are no experimental tools available for humans to examine key events, and therefore, there is a need to start a new trend of examining and identifying key events in humans during the investigation of any human toxicological exposure in order to better use the huge bank of animal data available and thus, to support or refute assumptions based on this data. To start a new paradigm, studies that are specifically designed to develop tools for identifying or testing key events have to be initiated and then findings should be implemented in real exposure events. Key events are very important in the human risk assessment process, and if toxicological studies consider the identification of key events in animals only, then assessing risk in humans will stay imperfect.

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Conflict of interest

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