International Colloquium on Gap Junctions and Cancer

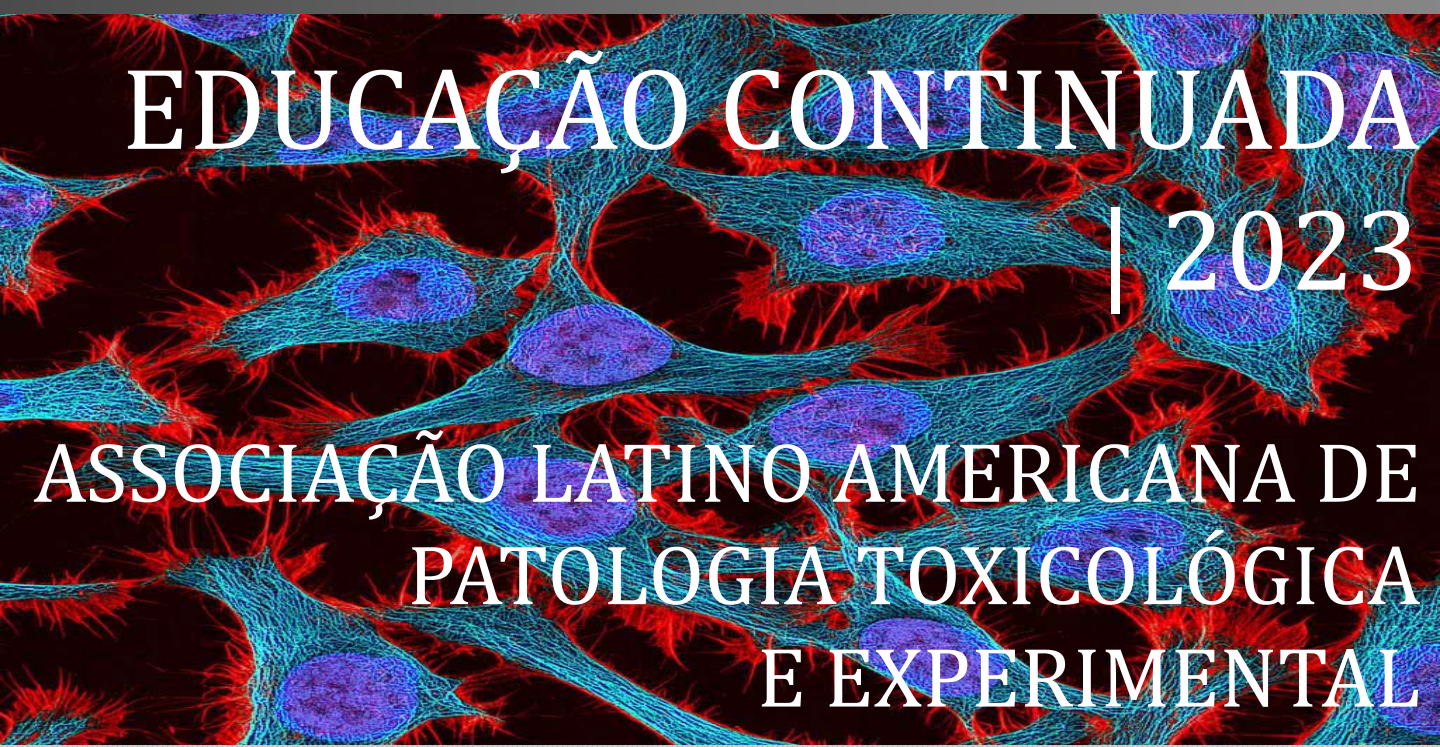
Regulatory Toxicology and Pharmacology

Regulatory Toxicology and Pharmacology 134 (2022) 105235

10% Body weight (gain) change as criterion for the maximum tolerated dose: A critical analysis

Reply to Letter to the Editor

ALAPTE



EDUCAÇÃO CONTINUADA | 2023

ASSOCIAÇÃO LATINO AMERICANA DE PATOLOGIA TOXICOLÓGICA E EXPERIMENTAL

Regulatory Toxicology and Pharmacology 139 (2023) 105366

Contents lists available at ScienceDirect

Regulatory Toxicology and Pharmacology

journal homepage: www.elsevier.com/locate/yrtph

Reply to Letter to the Editor

Rebuttal to the letter to the editors regarding Van Berlo et al. (2022) paper titled "10% body weight (gain) change as criterion for the maximum tolerated dose: A critical analysis"

We read with interest the comments of Berry et al. (*2023*) on our paper titled "10% Body weight (gain) change as criterion for the maximum tolerated dose: A critical analysis" (Van Berlo et al., 2022) and welcome discussion on this topic. Surprisingly though, the letter to the editor by Berry et al. is not so much a reaction on our analysis as it is a discourse on the rodent cancer bioassay, culminating in a plea for its retirement. We strongly object to the letter giving the impression that our paper is about the (need for the) rodent cancer bioassay, and about improving the predictivity/performance of this assay by increasing animal use and suffering and testing at exaggerated dose levels. This is not at all the message of our paper; it concerns the analysis that 10% body weight *gain* change is not a criterion for excessive toxicity. The addition of "gain" to "body weight change" is a scientifically unfounded modification of pre-existing carcinogenicity guidance that occurred without appropriate notification or discussion. Thus, it should not be used in setting and evaluating dose levels in toxicity testing, whether for carcinogenicity or for non-carcinogenicity endpoints. Hence, most reasons presented by Berry et al. to disagree with our paper are not relevant to the topic addressed. Nevertheless, some of the remarks made in the letter require a response.

Toxicity testing is about finding out what happens when homeostasis *starts* to be perturbed or when biological stress *starts* to be induced, and what adverse effects this results in at what dose. This can only be identified by using a sufficiently high top dose, and that is what is advocated for in our paper. With sufficiently high we definitely do not mean excessively high, as implied by Berry et al. Key is the word 'starts', and it goes without saying that we agree with the authors of the letter that exaggerated dose levels causing major homeostatic disruption or overwhelming of the metabolic systems, with severe suffering or death in the animals, is a no-go. But preventing any perturbation, pathological finding or e.g. any triggering of cell proliferation (as mentioned in the comments) to occur, goes against the very purpose of toxicity testing and greatly reduces the usefulness of these tests for human hazard and risk assessment. Moreover, from an animal welfare and ethical perspective this is unacceptable because it leads to a waste of valuable animals.

In agreement with Berry et al., and as also acknowledged in our paper, body weight is one of several pieces of information that need to be considered in dose-setting and MTD evaluation. With respect to body weight, Berry et al. remark that a 10% reduction in body weight gain may or may not be a reliable indicator that the MTD is achieved, thereby implying that such a reduction could already be considered excessive toxicity. In our paper we have clearly shown that a 10% reduction in body weight gain, which corresponds to less than 3% body weight reduction at the end of a 90-day toxicity study, is not a biologically relevant effect and thus far from (excessive) toxicity. Even a dose causing a 10% body weight reduction at the end of a 90-day toxicity study is shown not to be seen as excessive toxicity, reason why we have argued that the 10% body weight reduction criterion (let alone the 10% body weight *gain* reduction criterion) is not an appropriate MTD criterion in toxicity testing. For carcinogenicity testing, but not for testing other endpoints, we have however in our paper expressed support for the original criterion in guidelines for rodent cancer bioassays that the dose causing a 10% body weight reduction at the end of a 90-day toxicity study can possibly serve as a sufficiently high top dose in a carcinogenicity study. The origin of this criterion has nothing to do with avoidance of (excessive) toxicity, but with avoidance of false negative outcomes in the carcinogenicity study. As pointed out in our paper and also by a.o. Haseman et al. (*1997*), reduced body weights in dosed animals may mask the detection of carcinogenic effects. Haseman et al. (*1997*) therefore remark that "… (in) designing long-term rodent carcinogenicity studies, measures should be taken to minimize potential weight differences between doses and control groups …". Although these authors do not specify what the maximum body weight difference should be, it is likely that for that purpose the 10% body weight reduction criterion ended up in the original guidelines for rodent cancer bioassays.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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DOI of original article: https://doi.org/10.1016/j.yrtph.2023.105362.

https://doi.org/10.1016/j.yrtph.2023.105366

Available online 20 February 2023

Regulatory Toxicology and Pharmacology 139 (2023) 105366

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Handling Editor: Dr. Martin Van den berg