

# Statistical inference under order restrictions with applications to toxicology

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*Abstract:* The US National Toxicology Program (NTP) routinely conducts carcinogenicity studies, which expose rodents to different doses of a chemical under investigation. The NTP researchers are interested in detecting trends in tumor rates across dose groups. Using tumor incidence data obtained from the current bioassay, along with control data from past experiments (known as historical control data), the NTP researchers want to determine if there is a dose-related trend in tumor incidence. An important feature of the NTP cancer bioassay data is that in addition to the risk of developing cancer, animals are subject to the risk of early death (not necessarily due to cancer). Although a formal survival-adjusted test is available for analyzing the current bioassay data, until now there did not exist a satisfactory test that formally incorporates the historical control data while adjusting for survival differences. Using order restricted inference techniques, we propose a survival-adjusted test for detecting dose-related trends in tumor incidence rates that incorporates data on historical control rates and formally accounts for variation in these rates among studies. An extensive simulation, based on a wide range of realistic situations, demonstrates that the proposed test performs well in comparison to the current NTP test, which does not incorporate historical control data. In particular, our test can aid in interpreting the occurrence of a few tumors in treated animals that are rarely seen in controls.