Evaluating Stimulatory Cell Proliferation in Anticancer Drug Dose-Responses

Marc A. Nascarella[1], Edward J. Stanek, III[2] , and Edward J. Calabrese[1]

Environmental Health Sciences Program[1], and Biostatistics and Epidemiology Program[2]

Department of Public Health, University of Massachusetts, Amherst, MA

INTRODUCTION

We present an analysis of the National Cancer Institute (NCI) database on concentration-response relationships resulting from the evaluation of 2,189 candidate anticancer agents evaluated on 13 yeast (*Saccharomyces cerevisiae*) strains, resulting in 28,457 replicated concentration-responses. A previous analysis of these data has shown that the responses below the toxic threshold were poorly predicted by a threshold concentration-response model as defined by the use of a Bench Mark Dose (BMD), and a better fit by a biphasic or hormetic concentration-response model (Calabrese et al., 2006). This initial study evaluated the individual responses of concentrations and their replication below estimated BMDs, however it did not explore the individual concentration-response relationships. In addition, the initial study did not explore the issue of the magnitude of stimulation with respect to hormesis. This presentation extends the initial work by addressing each of these limitations. We determined the quantitative features of the hormetic concentration-responses (n = 4,407) using a previously published entry and evaluative criteria for inverted U-shaped concentration-responses. The quantitative features of the hormetic curves that are described are: (1) the width of the concentration range showing stimulation above 10% of the control, (2) the maximum stimulation of the hormetic concentration-responses, and (3) the width from the maximum stimulation to the zero equivalence point. These data are compared across the 13 different yeast genotypes, as well as with previously reported quantitative features of other chemical agents displaying hormetic concentration-responses evaluated on various endpoints and model organisms. These results show that 51.4% of the 2,189 anticancer agents evaluated display hormetic dose-responses in the 13 NCI yeast strains used as models for human cancers.

METHODS

NCI Laboratory Methods

The laboratory methods for the NCI Yeast Anticancer Drug Screen have been described previously (see Materials and Methods in Calabrese et al., 2006). Briefly, we used publicly available "stage 2" data that included 2,189 anticancer agents evaluated in duplicate over a 100-fold, semi-log spaced dose range consisting of doses of 1.2, 3.7, 11, 33, and 100 μM in 13 genetically unique yeast (*Saccharomyces cerevisiae*) strains (NCI, 2006). The endpoint measured was the growth of the anticancer agent exposed yeast strain relative to the same strain grown in a concurrent solvent control.

Selection of Hormetic Dose-Responses

We used an *a priori* entry criteria to evaluate the NCI stage 2 database that includes 28,457 individual dose-response curves. This process ensured that dose-responses displayed evidence of low dose stimulation followed by higher dose inhibition, displaying a characteristic inverted U-shaped dose-response (Figure 1). To ensure this both a maximum inhibitory response (≤80% of the control) and a minimum stimulatory response (≥110% of the control) were established. These values were consistent with a typical hormetic dose-response curve (Calabrese and Blain, 2005).

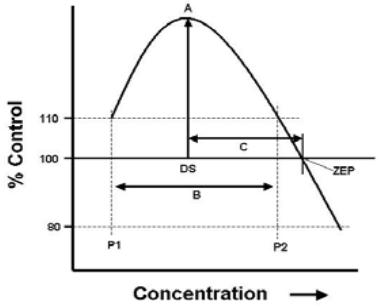


Figure 1. Parameters of the hormetic concentration-response curve that were assessed. (A) The maximum stimulatory response. (B) The width of the stimulatory response was calculated from the lowest (P1) to the highest (P2) concentration showing a response 110% of the control response. (C) Distance from the concentration of the maximum stimulatory response (DS) to the highest concentration with a response equal to the control (or the zero equivalent point [ZEP]).

RESULTS

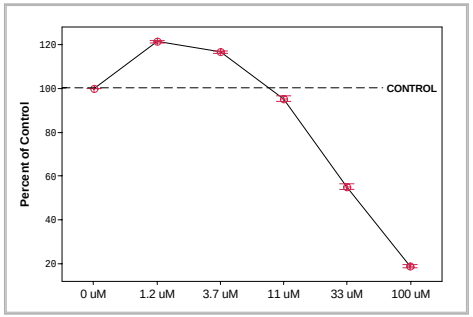
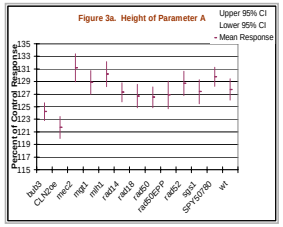
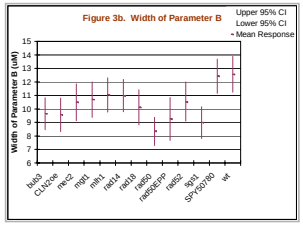


Figure 2. Composite concentration-response curve from the 4,407 hormetic concentration-response curves. Shown above is the mean response (and 95% CI) at each of the 5 concentrations used in the assay.





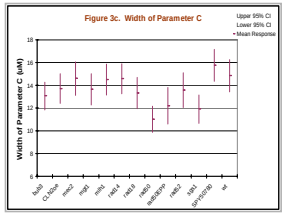


Figure 3. Results of measuring the individual parameters of the 4,407 hormetic concentration-response curves shown in Figure 1. Results are reported for the 13 different yeast strains. (a) The Maximum stimulatory response (mean = 127.5%). (b) The width of the stimulatory response from the lowest to the highest concentration showing a response 10% greater than the control response (mean = 10.4 μM). (c) Distance from the concentration of the maximum stimulatory response to the highest concentration with a response equal to the control (mean = 13.6 μM).

DISCUSSION

The results presented here are in general agreement with previous reports of over 5,600 hormetic concentration-response relationships from over 900 diverse chemical and physical agents (Calabrese and Blain, 2005). The amplitude of the stimulatory response is modest and is generally 30% greater than the control response. The mean width of the stimulation was found to be only 10.4 μM with 75% of the data below 14.4 μM. In fact, in our evaluation of the hormetic concentration-responses the width of stimulatory response extended on average from 2.4 μM (P1) to 12.8 μM (P2) resulting in a 5.3-fold width of stimulation. This is less than the 10-fold width typically observed in hormetic concentration-responses observed with other chemical agents and model organisms. However, it has been previously noted that the more homogeneous the population is, the narrower the range of the stimulatory response (Calabrese and Blain, 2005). The mean distance from the maximum stimulatory response to the ZEP is approximately within the normal reported value of 3- to 6-fold (Calabrese and Blain, 2005) given that the average value of this width was 6.7-fold. This was calculated given an average ZEP of 18.28 μM and an average stimulatory concentration (DS) of 2.7 μM. These data raise the important question that at low-doses anticancer agents may actually stimulate the proliferation of cancer cells (Calabrese, 2005).

REFERENCES

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