1 **HORMESIS COMMONLY OBSERVED IN THE ASSESSMENT OF**
2 **ANEUPLOIDY IN YEAST**

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ABSTRACT

Extensive dose response studies have assessed the potential of toxic chemical agents to induce aneuploidy in the yeast model. An assessment of such findings revealed that hormetic-like biphasic dose responses were commonly observed. A preliminary estimate of the frequency of the hormetic responses using *a priori* entry and evaluative criteria was approximately 65-80%. These findings suggest the possibility of hormetic effects being extended to genotoxic endpoints.

CAPSULE: This work is of significance because it provide substantial evidence that hormetic dose responses maybe applicable to genotoxic endpoints.

KEY WORDS: hormesis, biphasic dose response, aneuploidy, genotoxicity, yeast

1. INTRODUCTION

The evaluation of chemically induced errors in meiotic chromosomal segregation has had a complex history. In contrast to mutagenic effects which were studied since the late 1920s for radiation and since 1946 for chemicals, the assessment of environmental influences on meiotic chromosomal segregation was slow to follow. This gap in research activity was due to several factors, most important being the lack of evidence correlating environmental pollution either to trisomy 21 or to spontaneous abortion (Sankaranarayanan, 1979). Secondly, the frequency of spontaneous abortions within humans had been significantly underestimated. Finally, during the formative period of genetic toxicology, a genetic system in mammals was not available to facilitate an extensive and systematic study of this general area of concern. This situation lead researchers to investigate chemically induced non-disjunction responses via yeast meiosis (Parry, 1977; Parry et al., 1979). The yeast model permitted the identification of two types of abnormal meiotic events: proper non-disjunction that leads to disomic gametes and failure to complete chromosome set separation (failure of meiosis I or meiosis II, which result in diploid gametes). Since the yeast model was (1) stable in both the haploid and diploid states, (2) had relatively good tolerance of aneuploidy and polyploidy and (3) could display high frequency of sporulation under specific conditions, it became widely used as an experimental model. The present paper explores how the yeast model has been employed to assess the capacity of chemical agents to induce aneuploidy in the yeast model and its dose-response features. Of particular interest is that investigations in this area commonly employed large numbers of doses over a broad dose range, often including doses below well-defined toxic thresholds. This unique approach for assessing

chemically-induced aneuploidy in yeast provided an opportunity to assess whether biphasic dose responses may occur as predicted by the hormetic dose response model.

2. HORMESIS AND ANEUPLOIDY

2.1 Diploid and Disomic Meiotic Products

During the 1980s Sora and colleagues (Sora, 1985; Sora and Bianchi 1982; Sora and Carbone, 1987; Sora and Magni 1988; Sora et al., 1982, 1983, 1986, 1988) screened a number of chemicals for their capacity to induce disomic (i.e., having an extra chromosome in the haploid state that is homologous to an existing chromosome in this set) and diploid meiotic products in *Saccharomyces cerevisiae*. Their test system was based on selection of clones heterozygous for six markers on the right arm of chromosome V. The experimental procedure employed the selection of meiotic products carrying two copies of chromosome V and which are consequently prototrophic for the nutritional requirement specified by markers located in alternate trans positions along the right arm of chromosome V. The use of these markers facilitated a determination of whether observed disjunctions occurred at meiosis I or II. The origin of diploid meiotic cells resulted from a failure of the second meiotic division (Sora et al., 1982). The spontaneous diploid frequency following meiosis is $5/10^3$ spores. With respect to chromosome V disomy the overall spontaneous frequency was $0.95/10^4$ viable spores with a 2:1 ratio of disomy of meiosis I to meiosis II.

The screening of numerous compounds using the *S. cerevisiae* system revealed that agents could enhance as well as reduce the occurrence of diploid and/or disomy conditions. In fact, in their first screening assessment they identified three agents (i.e.,

76 propranol, atenolol, trifluoperazine) that reduced the occurrence of non-disjunction while
77 caffeine enhanced this response (Sora and Bianchi, 1982). This mechanistic oriented
78 screening experimentation suggested that the increased induction of the diploid condition
79 by caffeine may be related to an increase in cyclic AMP levels.

80 The research of Sora has particular relevance to the hormesis hypothesis since
81 these experiments commonly employed from 5-9 doses with dose spacing usually being
82 two-fold at the lower doses and less than two-fold as the doses increased. This type of
83 dose spacing was advantageous in the possible assessment of hormetic dose responses
84 since it would permit a detailed assessment of the dose response in the low dose range
85 while at the same time reducing the chances of missing a potential biological response
86 (Calabrese, 2008; Calabrese and Blain, 2005, 2011). Of further value was that the data
87 also typically provided information on the variability of the historical control group for
88 each endpoint in each experiment. Typically each experiment evaluated the frequency of
89 sporulation, diploids, disomy and mutational recombination. In order to measure these
90 endpoints the yeasts were grown on different media. For example, in the case of
91 mutational recombination the media was deficient in histidine and threonine. Surviving
92 cultures have been assumed to have acquired mutations that permit the synthesis of these
93 essential amino acids.

94 In their survey of several dozen agents, Sora and colleagues assessed inorganic
95 and organic chemicals, some of which have considerable environmental relevance. While
96 the authors were principally concerned with the identification of agents that could
97 increase non-disjunction responses, they noted that multiple compounds were able to
98 decrease the occurrence of non-disjunction. They indicated that KCl reduced the

99 occurrence of non-disjunction by decreasing the frequency of disomic spores. A similar
100 decrease also occurred with respect to the formation of diploids though it was not
101 mentioned by the authors. The authors also noted that mutational recombination was
102 reduced in KCl treated yeast (Sora et al, 1986). In each of these cases the dose response
103 followed an hormetic dose response pattern with a low dose inhibition followed by an
104 increase in non-disjunction or mutations at the higher doses. KCl also induced an
105 hormetic-like biphasic dose response for sporulation. Similar dose responses were also
106 reported for a number of other agents tested, including, for example, chloral hydrate,
107 ethidium bromide (Sora and Carbone, 1987) (Figure 1), epichlorohydrin, hycanthone
108 (Sora, 1985) (Figure 2), cadmium chloride (Sora et al., 1986, 1988) (Figures 3 and 4) and
109 others (Figures 5-9). However, in these cases the authors did not acknowledge the
110 possibility of a low dose for such genotoxic agents decreasing the occurrence of non-
111 disjunctional endpoints or mutational recombination.

112 The hormetic dose responses were observed to occur for both diploid and disomy
113 non-disjunctional endpoints. In some cases an hormetic response occurred for both
114 endpoints when tested at the same concentrations by the same chemical (e.g., chloral
115 hydrate, ethidium bromide) (Sora and Carbone, 1987). However, it was not uncommon to
116 find that the hormetic response occurred for either disomy or diploid formation but not
117 both. In these cases it is not known whether an hormetic response may have occurred at a
118 lower dose of the endpoint that did not display an hormetic response since these
119 responses were still in a high dose response zone.

2.2. Chromosomal Malsegregation

Other authors have reported data indicative of hormetic dose responses within the yeast model for chromosomal malsegregation (Albertini, 1991; Zimmermann and Mohr, 1992, Elhajouji et al., 1997). For example, hormetic-like biphasic dose responses were reported with benomyl, EMS (Figure 7) and MMS (Figures 5 and 7) by Albertini (1991) and for ethyl dibromoacetonitrile and 2-hydroxypropionitrile (Figure 6) (Zimmermann and Mohr, 1992). Mutation frequency was also decreased in an hormetic manor in the yeast model by bavistan (Figure 7). However, these hormetic-like biphasic dose responses were not noted in the paper. Likewise, hormetic-like dose responses have been reported with human lymphocytes (chromosomes 1 and 17) for several spindle inhibitors (i.e., mebendazole, nocodazole, and a standard reference clastogen, MMS (Figure 5) (Elhajouji et al., 1997). In this study statistical analyses were presented for doses that significantly increased the occurrence of chromosomal non-disjunction. It is not clear whether the consistent decreases observed for chromosomal non-disjunction achieved statistical significance. While Elhajouji et al. (1997) proposed a threshold mechanism of action for mebendazole and nocodazole, their data appear consistent with both hormetic and threshold dose responses.

Whittaker et al. assessed the capacity of various chemicals to induce chromosomal non-disjunction using the diploid yeast strain BR 1669 of *S. cerevisiae* (Whittaker et al., 1989, 1990) (Figures 8 & 9). This strain can detect spontaneous and induced chromosomal VIII gain (hyperploidy) in mitotic and meiotic cells. This system detects increased gene dosage at two linked loci, *arg4-8* and *cup1^S*, located on chromosomal VIII. The experiments generally employed 6-9 doses which were intended

to be in the region of maximum aneuploidy induction on the dose-response (survival) curve. The critical doses were to lie between the highest dose that fails to inhibit growth (i.e., sporulation) and the lowest dose that leads to total inhibition growth (i.e., sporulation). Replication experiments were conducted/reported if the first trial induced a strongly positive response. The authors also employed a cold intervention procedure for some experiments as this procedure can maximize aneuploidy induction. While the intent of the research was to assess the potential of selected chemicals to induce aneuploidy, hormetic responses were commonly observed for prototroph frequency (e.g., methyl benzimidazol-2-YL carbamate, mitotic trial I; propionitrile, mitotic standard trials I & II, cold interruption mitotic trials I & II; cyclophosphamide monohydrate, meiotic trial II; methyl methanesulfonate, meiotic trial I). Careful review of the replication experiments indicated large differences in control values, as well as in treatment effects, thereby supporting a decision to view each experiment as an independent study.

Hormetic responses also were seen for direct counts of yeast cells (e.g. methyl benzimidazole-2-YL carbamate – meiotic trials I & II; DMSO – mitotic trial I; propionitrile – meiotic trial I) and for sporulation and direct colony counts (methyl methanesulfoxinate – meiotic trial I) (Figure 8). In the study by Whittaker et al. (1990) no mention was made of hormetic-like biphasic dose responses regardless of the endpoint or chemical. While there may have been uncertainty for some of the possible hormetic dose responses, hormetic-like responses for colony counts for methyl benzimidazole-2-YL carbamate and the sporulation efficiency and direct yield colony counts for MMS appeared substantial.

3. SPORULATION

In yeast non-disjunction experiments sporulation has been typically measured. The non-disjunction frequency is often measured between the dose-boundary of when sporulation starts to decrease to when it is eliminated. Consequently, it has not been of explicit interest to assess the nature of the dose response continuum for sporulation although earlier reports have indicated that hormetic-like biphasic dose responses may occur (Arnaud and Galzy, 1973). In broad screening studies non-disjunction evidence suggestive of a possible threshold has been reported (e.g., Be(NO₂)₂, MnSO₄, Cl₂, bleomycin, MMS, caffeine, and chloral hydrate) while hormetic-like biphasic effects have been reported for other agents [e.g., KCl, CdCl₂, Sora et al., 1986 (Figure 3); VOSO₄, Sora et al., 1986 (Figure 3); CdCl₂ and caffeine, Sora et al., 1988 (Figure 4)]. Enhanced sporulation does not appear to be consistently associated with a decrease or increase in mutational recombination or with non-disjunction (i.e., disomy or diploidy). In general, follow up studies have not been directed to assess underlying hormetic mechanisms for the above causes of sporulation as well as its biological implications.

4. RECOMBINATIONAL MUTATION

Mutational recombination has typically been assessed in non-disjunction experiments with yeast. Hormetic responses for non-disjunction have typically not been strongly associated with similar biphasic dose responses for mutation. While the occurrence of hormetic effects for recombinational mutation appears to be as common as hormetic non-disjunctional effects, they may or may not occur with the same agents during the same experimental conditions. While these data suggest the occurrence of

independent biological processes, no focused research has been directed to clarify their inter-relationship. Resnick et al. (1986) indicated that the frequency of aneuploidy is increased in diploids homozygous for mutations that result in faulty recombination events (Kunz and Haynes, 1982). These observations suggested that treatments that enhanced mutational recombination may also increase the frequency of aneuploidy.

5. FREQUENCY OF HORMETIC RESPONSES IN YEAST ANEUPLOIDY STUDIES

The assessment of chromosomal non-disjunction and supplementary endpoints (e.g., sporulation, recombination mutation) has been studied extensively in the yeast model. These studies have been characterized by the use of a relatively large number of doses, typically ranging from 5 – 10. This dose range has been framed within the dose response of the sporulation endpoint, ranging from the lowest significant decrease to the dose which reduces sporulation by approximately 100%. This provided opportunities to assess the effects of possible chemical aneuploids over a broad dose range. The spontaneous occurrence of non-disjunction responses such as diploidy or disomy within the yeast model (DIS13 strain – Sora et al., 1982, 1983) was $1.05/10^4$ viable spores and $0.68/10^4$ viable spores, respectively. The spontaneous recombination frequency was $1.7/100$ viable spores (Sora, 1985). The spontaneous sporulation frequency was approximately 55-80%. Of particular interest is that the control group standard deviation (SD) for diploidy and disomy across strains was relatively low approaching 20% of the control mean. However, some studies exceeded 50% of the control mean. In the case of

recombination and mutations the SD was generally consistent, being about 20-27% of the mean.

Since in the case of sporulation, a control would typically display a frequency value between 55%-80%, this permits the possibility to assess a modest hormetic region/range above controls since the maximum increase would be capped at 100%. In cases of recombinational mutation and non-disjunction the response would be viewed within a J-shaped dose response. Based on background variation it is likely that the recombination effects may be more reliably studied. These endpoints display a more consistently lower background variation and higher frequency (1-2%) than the non-disjunction endpoints. Despite the concern for variation in background non-disjunction responses, review of individual dose responses indicates less variation within rather than between studies. Based on these observations, replication studies were considered more valuable with respect to qualitative rather than quantitative assessment.

5.1. Estimation of Hormesis Frequency for Aneuploidy

Based on the studies cited in this paper a preliminary estimate of the frequency of hormetic responses for aneuploidy based on the findings of Sora (Sora 1985; Sora and Carbone, 1987; Sora et al., 1986, 1988) was made using *a priori* entry and evaluative criteria. The Sora findings were selected because of their extensive nature, broad range of chemical classes assessed consistency in the research methodology, as well as analysis in the presentation/analysis of data and focused specialization of the journals in which their papers were published (i.e., Mutation Research, EMM and Mutagenesis). The entry criteria followed the method of Calabrese et al., (2006), with each dose-response being required to have a bench mark dose (BMD)₁₀ (i.e., 10%

increase in aneuploidy effect greater than controls) that was bounded by a lower dose with a response less than the BMD10 and an immediate dose with a response greater than the BMD10 response. The lower bounding dose could not be used to estimate the response of doses below the BMD10. There was the additional requirement for at least one dose below the BMD10 lower bound (LB) dose. The evaluative criteria for a positive hormetic conclusion for a dose response generally followed those used by Calabrese and Blain (2005, 2011) for the hormesis data basis. The use of the local/bounded BMD10 makes it significantly more difficult to satisfy the evaluative criteria for an hormesis determination. For a dose-response to be designated as displaying hormesis, at least one response to a dose below the BMD10 LB dose had to have a response $\leq 90\%$ of the control group. The findings indicate that there were 141 total dose responses available for evaluation. Of the 141 dose responses, 26 (18.4), satisfied the entry criteria. These 26 dose responses had a total of 75 response doses below the BMD10 LB with 48 (64%) satisfying the *a priori* evaluative criteria of a response $\leq 90\%$. A complementary assessment considered the proportion of dose responses that satisfied entry criteria that displayed at least one response to a dose below the BMD10 LB $\leq 90\%$. Of the 27 dose responses satisfying the entry criteria 22 (81.4%) satisfied this evaluation.

The present evaluation represents a preliminary attempt to explore the nature of the dose response below a traditional toxicological threshold for chemically-induced non-disjunction. This was undertaken as part of a general research goal to assess the occurrence of hormetic responses with respect to genotoxic endpoints. The findings indicate that many agents induced J-shaped dose response consistent with the hormesis hypothesis. Despite the many examples that were observed in data tables, only one paper

(Sora and Bianchi, 1982) explicitly affirmed the J-shaped response for non-disjunction endpoint and for recombination. Nonetheless, the quantitative features of these specific J-shaped responses were consistent for non-disjunction endpoints which other investigators failed to note.

6. CONCLUSIONS

The present paper represents what is believed to be the first attempt to explore the possibility of hormetic dose responses for aneuploidy. The data availability using the yeast model were robust with respect to the number of doses used in specific experiments, thereby creating the opportunity to assess the nature of the dose response in the low dose zone. In general, the findings reveal that hormetic-like biphasic dose responses were common with average responses in the hormetic zone [i.e., doses below the BMD10 lower bound (LB) value] within 50% to 80% of the control value (Figure 10) for four doses below the LB dose, findings consistent with that reported in the hormesis database (Calabrese and Blain, 2011). While the findings presented in the present paper were dominated by a limited number of investigators several decades ago, they are quite robust. They offer the potential for current researchers to explore the mechanistic basis of such hormetic – biphasic dose responses as highlighted in the review by Mulla et al. (2014) on yeast and aneuploidy. Furthermore, it is hoped that the robustness of these findings in the yeast model will stimulate the assessment of dose-response features for aneuploidy in various mammalian cell cultures in order to assess the broader generality of the findings presented here with yeast.

While findings presented involve the use of the yeast experimental model, substantial epidemiological efforts have assessed the occurrence of aneuploidy among the children of the survivors of the atomic bombing of Hiroshima and Nagasaki based on a function of the combined parental doses (Neel et al., 1990; Schull, 2003). Of a total of 16,298 children studied with about half the total being controls, a background aneuploidy incidence of 0.29% was reported. The overall dose response was J-shaped, with no cases of aneuploidy occurring in the lowest dose group of 1,346 subjects, while 4 would have been expected. While these findings are consistent with the hormetic dose response a cautious perspective is needed given the well-recognized limits of epidemiological investigations (Taubes and Mann, 1995). While the collective experimental findings are limited to the yeast model and of a preliminary nature, they reveal both a substantial occurrence and high frequency of hormetic-like biphasic dose responses. These findings are generally consistent with other efforts to assess the frequency (Calabrese and Baldwin 2001, 2003; Calabrese et al., 2006, 2008, 2011, 2012) and the quantitative features (Calabrese and Blain 2005, 2011) of hormetic dose responses. These novel findings are of interest since they suggest the need to explore whether hormetic effects may be commonly observed for other genotoxic endpoints.

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Figure 1. Hormetic Responses and Chromosomal Non-Disjunction and Diploid/Disomic Meiotic Products in Yeast (Source: Based on Sora and Carbone, 1987)

Figure 2. Hormetic Responses and Chromosomal Non-Disjunction and Diploid/Disomic Meiotic Products in Yeast (Source: Based on Sora, 1985). Note: Where data are not plotted, they exceed the upper dimensions used in the graph.

Figure 2. (Continued)

Figure 2. (Continued)

Figure 3. Hormetic Responses and Chromosomal Non-Disjunction and Diploid/Disomic Meiotic Products in Yeast (Source: Based on Sora et al., 1986)

Figure 3. (Continued)

Figure 3. (Continued)

Figure 3. (Continued)

Figure 3. (Continued)

Figure 4. Hormetic Responses and Chromosomal Non-Disjunction and Diploid/Disomic Meiotic Products in Yeast (Source: Based on Sora et al., 1988)

Figure 4. (Continued)

Figure 5. Hormetic Responses and Chromosomal Non-Disjunction (ND) and Diploid/Disomic Meiotic Products in Yeast (Source: Based on Elhajouji et al., 1997)

Figure 5. (Continued)

Figure 6. Hormetic Responses and Chromosomal Non-Disjunction and Diploid/Disomic Meiotic Products in Yeast (Source: Based on Zimmermann and Mohr, 1992)

Figure 6. (Continued)

Figure 7. Hormetic Responses and Chromosomal Non-Disjunction and Diploid/Disomic meiotic Products in Yeast (Source: Based on Albertini, 1991)

Figure 7. (Continued)

Figure 7. (Continued)

Figure 7. (Continued)

Figure 7. (Continued)

Figure 8. Hormetic Responses and Chromosomal Non-Disjunction and Diploid/Disomic Meiotic Products in Yeast (Source: Based on Whittaker et al., 1990)

Figure 8. (Continued)

Figure 8. (Continued)

Figure 8. (Continued)

Figure 8. (Continued)

Figure 9. Hormetic Responses and Chromosomal Non-Disjunction and Diploid/Disomic Meiotic Products in Yeast (Source: Based on Whittaker et al., 1989)

Figure 9. (Continued)

Figure 9. (Continued)

Figure 9. (Continued)

Figure 9. (Continued)

Figure 9. (Continued)

Figure 10. An integrated meta dose-response assessment for the effects of chemicals on aneuploidy in yeast to estimate hormetic frequency (based upon the articles cited in this paper)