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Egg Selenium Thresholds for Birds: A Response to J. Skorupa's Critique of Fairbrother *et al.*, 1999

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There is no doubt that selenium causes embryo toxicity when present at sufficiently high concentrations in bird eggs. Subsequent reduced growth and survivability of ducklings may also result from selenium exposure. The current debate centers around how much selenium is required to cause these changes in a significant number of birds. In other words, what the dose-response relationships look like and which value should be selected for use in a regulatory context. In our paper (Fairbrother *et al.*, 1999), we suggested that an EC_{10} of 16 mg/kg (dw) mean egg selenium (MES) would be a reasonable value based on data from all controlled laboratory studies that have been reported in the peer-reviewed literature. Dr. Skorupa responded (Skorupa, 1999) that our conclusion is incorrect, as we arbitrarily excluded one data point and neglected to include data from an additional laboratory study, as well as information that he has collected from field studies. We appreciate Dr. Skorupa bringing to our attention the missed laboratory study, but will show that the data from that study are in accord with the others and, therefore, do not change the estimated EC_{10}. Furthermore, we will clarify why the excluded datum is inconsistent with all other points, suggesting something anomalous with the chemical analysis of selenium concentrations in these eggs. This highlights the necessity for careful examination of all data that are used to develop regulatory criteria, as unintentional errors might occur during sample analysis, study design, or data interpretation. Our experience in examining literature reviews and large data sets used to support threshold values for selenium in a regulatory context indicates a lack of consistency in data treatment and misinterpretation of primary literature with significant implications on threshold selection (*e.g.,* DeForest, Brix, and Adams, 1999). It is for these reasons, exemplified by our arguments about a flawed datum from a well-controlled laboratory study, that we continue to argue

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against using field data that have been reported only in government publications without the benefit of a full description of study design, data tables, treatment of potential confounding factors, and independent scientific peer review.

WHAT THRESHOLD DO LAB STUDIES REALLY SUPPORT?

Omission of the data from Stanley *et al.* (1996) in our previous analysis was due to an oversight and was not intentional. We agree with Dr. Skorupa that the data from this study should be included in the analysis for deriving an EC_{10}. A reanalysis of the data set with Stanley *et al.* (1996) data included indicates the estimated EC_{10} remains unchanged at 16 mg/kg (dw) MES (Figure 1). This illustrates the consistency of results among the various laboratory studies.

Dr. Skorupa also commented that we were unjustified in excluding a datum from the Heinz *et al.* (1987) study. We chose to exclude this value, because it is anomalous when compared with all other data points from the other studies, as is clearly demonstrated in Figure 2. Dr. Skorupa argues that the discrepancy between the results of Heinz *et al.* (1987), and the other studies is due to the variability in sensitivities of individual mallards and that it cannot be expected that replicated treatments of small groups will necessarily be any better than in rough agreement. However, there is consistency in results among the other four studies, which argues against Dr. Skorupa's expectation of high variability.

The Heinz *et al.* (1987) datum is so inconsistent with all other results that this single data point changes the calculated EC_{10} from 16 to 10 mg/kg (dw) MES; exclusion of any of the other data does not substantially alter the EC_{10}. Moreover, the large variability in the Heinz *et al.* (1987) datum is evident only when duckling mortality is described as a function of egg selenium concentration. When duckling mortality is plotted vs. dietary selenium, the variability in the dose response relationship between the four studies is quite small (Figure 3). This suggests that the mortality response is as expected and that an error may have occurred in the analysis of the selenium concentration in the eggs. Thus, we feel justified in excluding this datum from our derivation of the dose-response relationship based on egg selenium concentration. In our opinion, toxicity data always should be critically evaluated, particularly when data are being combined from multiple studies for use in a regulatory context.

Dr. Skorupa also commented that we combined incompatible endpoints from the various laboratory studies. The endpoint we used was cumulative duckling mortality as a percentage of all eggs laid (*i.e.*, including egg infertility and embryo mortality as an index of total reduction in potential population recruitment). Dr. Skorupa argues that it is inappropriate to combine data from Heinz, Hoffman, and Gold (1989) with data from the other studies because Heinz *et al.* (1989) fed ducklings clean food, while the other studies provided the ducklings with the same selenium diets that were fed to their parents. Contrary to Dr. Skorupa's assertion that we did not seem to be aware that we were comparing two qualitatively different endpoints, we chose to combine the data because there is no evidence that feeding ducklings selenium-amended diets results in mortality at the concentrations to which they were exposed in these studies. The highest dietary selenium concentra-

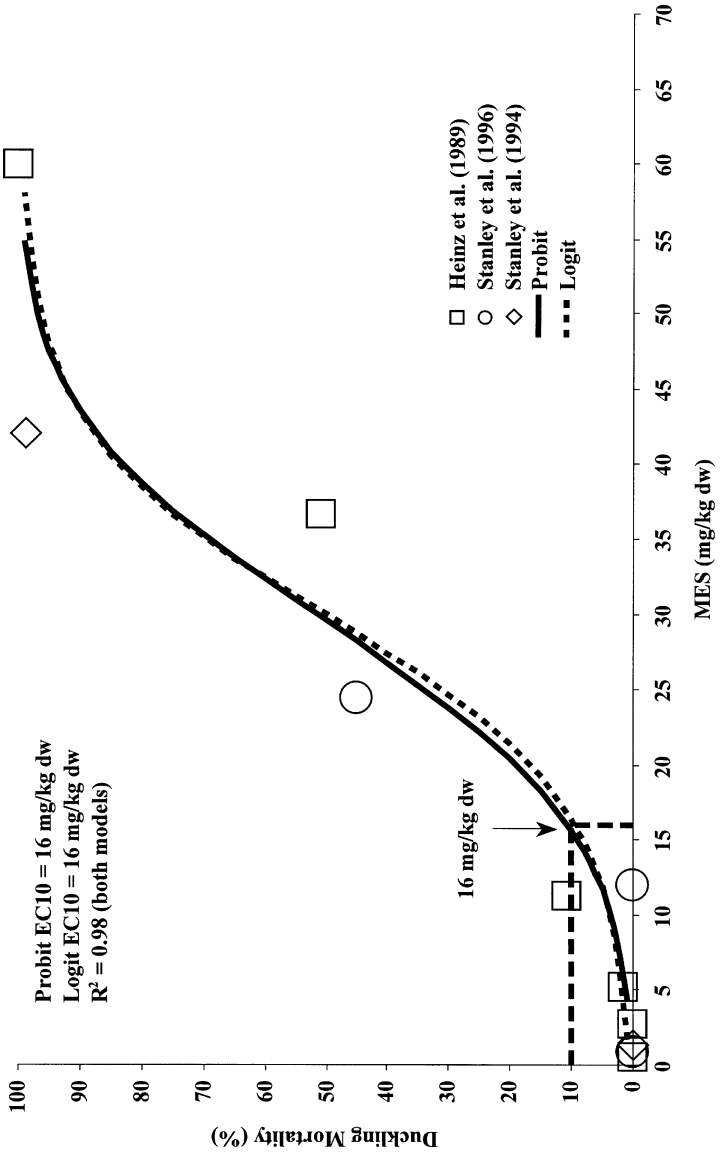

Figure 1. Relationship between MES and duckling Mortality using toxicity results from Heinz *et al.* (1989) and Stanley *et al.* (1994, 1996).

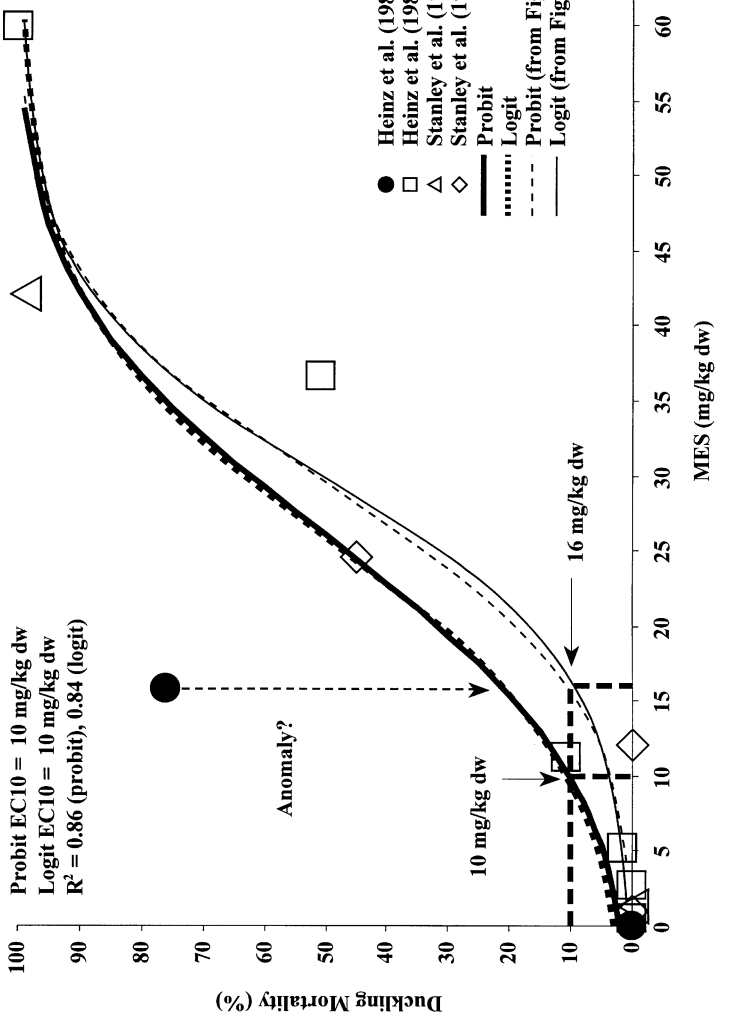

Figure 2. Relationship between MES and duckling mortality using toxicity results from Heinz *et al.* (1987), Heinz *et al.* (1989), and Stanley *et al.* (1994, 1996).

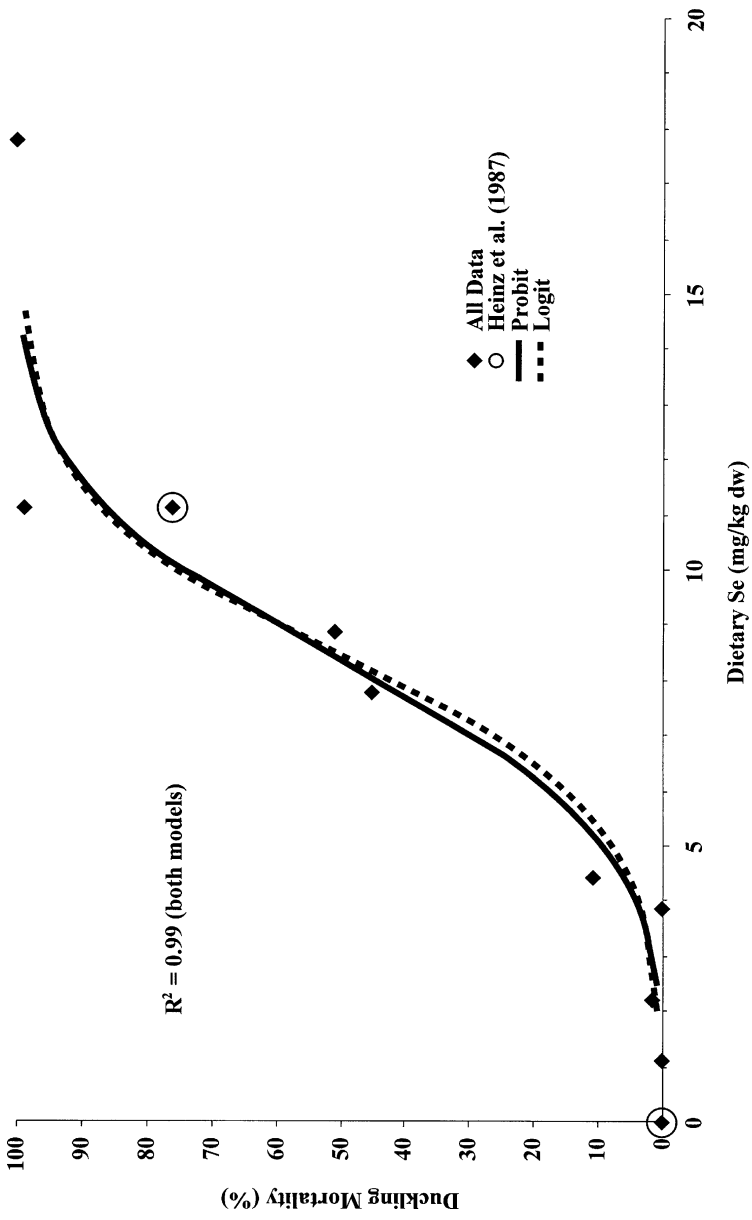

Figure 3. Relationship between Dietary Se and duckling mortality using toxicity results from Heinz *et al.* (1987), Heinz *et al.* (1989), and Stanley *et al.* (1994, 1996).

tion provided ducklings in any of the studies was 10 mg/kg dw (Stanley *et al.*, 1994). However, there was no mortality in ducklings fed 20 mg/kg dw for 6 weeks or 30 mg/kg dw for 2 weeks, when feeding was initiated at hatch (Heinz, Hoffman, and Gold, 1988; Heinz, Hoffman, and LeCaptain, 1996). It is possible, theoretically, that *in ovo* exposure to selenium predisposes ducklings to higher post-hatch mortality if placed on selenium-amended diets. However, given the low dietary concentrations provided we believe that duckling mortality in these studies is more likely a function of parental exposure and deposition of selenium into the egg. Regardless, if the Heinz *et al.* (1989) data are excluded and only data from Stanley *et al.* (1994, 1996) used in our analysis, the calculated EC_{10} for duckling mortality changes only slightly, increasing to 18 mg/kg (dw) MES (Figure 4). Therefore, we point out that the use of the combined data was not done by the authors to intentionally derive a high threshold, but to strengthen the data set.

IS EGG INVIABILITY MORE SENSITIVE THAN TERATOGENECITY?

Dr. Skorupa appears to have misinterpreted our comparison of the duckling mortality and teratogenesis concentration-response relationships. We simply compared the two concentration-response models and determined that they could not be differentiated statistically. Dr. Skorupa's comments imply that we stated that the two endpoints are equally sensitive and that there is an equal probability of percent egg inviability exceeding percent teratogenesis at any given egg selenium concentration. Dr. Skorupa tabulated egg inviability and teratogenesis data in order to demonstrate that egg inviability was a more sensitive endpoint than teratogenesis in five out of five cases. In fact, we agree with this assertion and go one step further in suggesting that cumulative mortality (*i.e.,* duckling survival to 7 to 14 days as a percent of total number of eggs laid) is likely to be the most sensitive endpoint, and stated: "despite being unable to statistically distinguish between the two endpoints, development of dose-response relationships does suggest that mortality is a more sensitive endpoint than teratogenicity." Consequently, the EC_{10} of 16 mg/kg (dw) MES that we recommended is based on the duckling mortality endpoint precisely for this reason.

FIELD DATA

Dr. Skorupa (1999) argues that we should give equal weight to the data he and others have collected from field studies of selenium-induced effects in black-necked stilts. He states that his methods accurately account for all potentially confounding effects that we identified. However, without access to a description of the study design and the environmental factors and contaminants that potentially confound field results of hatchability and nestling survival, it is not possible for us to conduct an independent critical review of Dr. Skorupa's results similar to what we have done with the laboratory studies. While it may be true, as argued by Dr. Skorupa, that eggs incubated in the laboratory accurately reflected hatching success of field populations for the 1 year of study, this only proves the lack of confounding field-related stress factors in that year. Without review of information regarding other years in

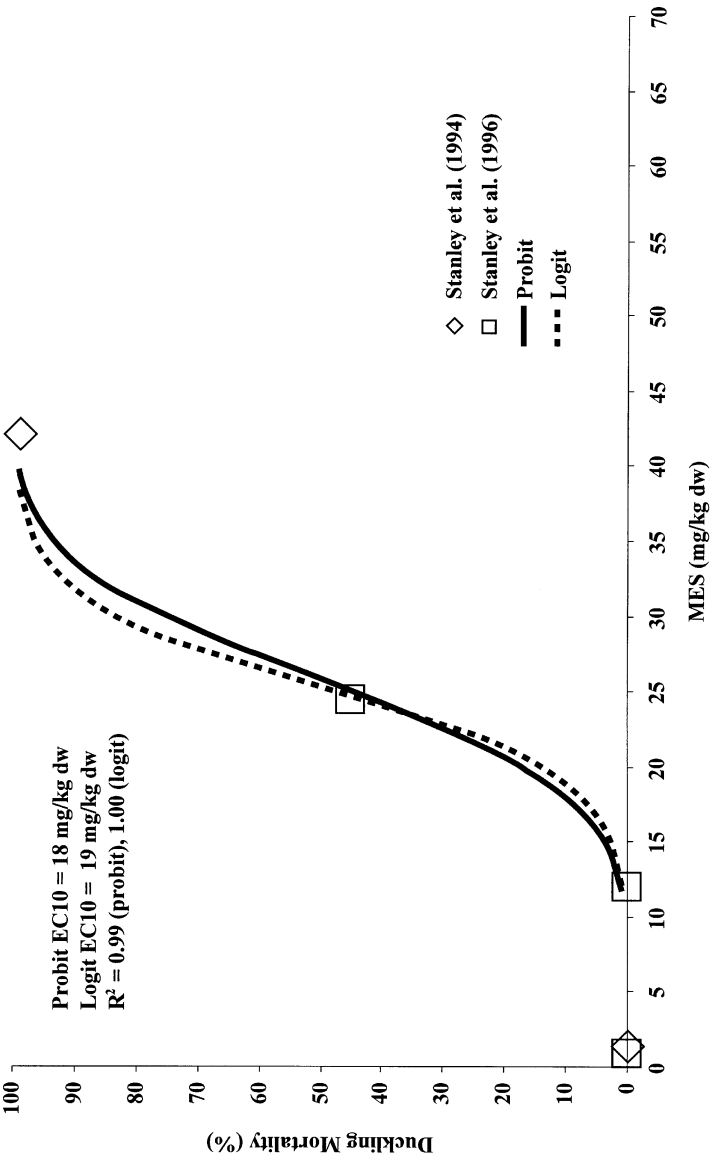

Figure 4. Relationship between MES and duckling mortality using toxicity results from Stanley *et al.* (1994, 1996).

which data have been collected, a similar conclusion cannot be reached. In our experience, for example, a storm event occurring at a critical time during the bird-nesting season can significantly reduce field hatchability in a manner that would not be replicated in eggs concurrently incubated in the laboratory. Thus, the laboratory study cited by Dr. Skorupa does not substantiate his claims for lack of confounding influences in his field studies from all years and locations (note, also, that the reference to the unpublished thesis by Martin in our paper was only in relation to our tabulation of effects of dietary selenium on avian responses as reported in any laboratory or field study).

An additional potentially important confounding factor with the use of field data in assessing toxicity is the potential for co-contaminants to occur, but not be evaluated. This becomes a very critical issue when field data are being used to establish a threshold for effect. It is precisely at this point in the dose-response curve where small changes in hatchability and chick survival (generic endpoints affected by many contaminants) are significant in terms of threshold selection. Dr. Skorupa argued that sufficient examination for co-contaminants has occurred to ensure this is not a concern. We disagree and point out that the references cited by Dr. Skorupa in support of this assertion do not cover the entire field data set used to derive the bird thresholds (Skorupa, 1998a, 1998b). We find no evidence in the published literature that a systematic examination of all eggs has occurred.

Dr. Skorupa, in his rebuttal of our paper, indicated that our request for his field data to be published in an independently peer-reviewed journal is "a red herring argument". We believe publication in a peer-reviewed journal is the proper approach for advancing the state of the science. The current government publications cited by Dr. Skorupa in support of field-derived avian thresholds lack the independence associated with a peer-reviewed journal. In Skorupa (1998a), for example, dose-response curves relating black-necked stilt and avocet teratogenesis to egg selenium concentrations are provided, but the figures do not include a (customary) plot of the data associated with the derived dose-response curves, nor is a table provided showing the egg selenium concentrations and associated levels of effects. In addition, Skorupa (1998a) contains a figure showing the dose-response curve for nest impairment in black-necked stilts which is the basis for his recommended egg selenium threshold of 6 mg/kg dw. However, the data set has been truncated showing only egg data in the 4 to 9 mg/kg dw range. Without presentation of the entire data set both graphically and in a data table, it is difficult to interpret this figure or assess the appropriateness of the statistics used to estimate the effect threshold. Presentation of the data in both of these formats is needed to properly evaluate the conclusions; without these additional data, the reader has to accept the threshold conclusions without the possibility of independent verification.

The government publications in which Dr. Skorupa has reported his results do not require nor contain the rigorous description of methods, data, and interpretation present in scientific journals. Dr. Skorupa argued that we previously used data from the NIWQP studies (*e.g.,* Adams *et al.*, 1998), thereby qualifying these publications as acceptable. We point out that we only used information provided about selenium concentrations in various media where raw data were available for review. To the best of our knowledge, a detailed description of the experimental design, field collection, chemical analysis, and presentation of the raw data for the egg

selenium-chick mortality relationship derived by Dr. Skorupa has never been published in a NIWQP report, any other report, or in the peer-reviewed literature. Therefore, consistent with the requirements for use of data in the development of water quality criteria (Stephan *et al.*, 1985), a similar regulatory context, we decline to use Dr. Skorupa's field-derived data on avian reproductive impairment until they can be verified independently.

CONCLUSION

Dr. Skorupa states that we do not provide scientifically credible evidence for proposing an avian response threshold different than those summarized by Heinz (1996) or Skorupa (1998a, 1998b). After reviewing Skorupa's comments and based on our responses above, however, we still believe that an EC_{10} of 16 mg/kg (dw) MES is scientifically defensible. In fact, this value is compatible with thresholds identified by other authors. Stanley *et al.* (1996), for example, state that the threshold for reproductive impairment in mallards occurs when selenium concentrations in eggs reach about 5 mg/kg ww, or 17 mg/kg dw (assuming an egg moisture content of approximately 70% as in Heinz *et al.*, 1989, Stanley *et al.*, 1996). As pointed out by Dr. Skorupa, Heinz (1996) summarized the literature available at the time and stated that a no-effect threshold for mallards is approximately 3.4 mg/kg wet weight (equivalent to 11 mg/kg dw). Dr. Skorupa suggests that this value may actually be closer to an EC_{10} as Heinz *et al.* (1989) demonstrated that hatchability of fertile eggs was reduced as compared with controls. However, Heinz *et al.* (1989) did not correct for a low hatchability (59.6%) in the control eggs. Additionally, it is not clear whether the Heinz (1996) recommendation is for individual mallard eggs or for the mean egg selenium concentration of a population of birds, as defined in our model. Therefore, we do not believe that our result is inconsistent with that of Heinz (1996). The primary strength of our analysis, however, is the derivation of a dose-response curve rather than reliance on interpretation of a threshold from application of an analysis of variance to test data. We argued strongly, and still believe, that the use of dose-response relationships in a regulatory context provides a much stronger basis for decision making, as such models clearly describe the level of protection being applied and the uncertainty associated with the assessment. Of course, all models are only as good as the data on which they are based, and we strongly endorse Dr. Skorupa's call for additional tests designed specifically to measure responses of avian embryos at low egg selenium concentrations.

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