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Senator Sheila Kuehl
10951 W. Pico Blvd, Suite 202
Los Angeles, CA 90064

Re: "Evaluation of retinoblastoma incidence in children in Los Angeles and Ventura counties," Report of the California Cancer Registry to Senator Kuehl

Dear Senator Kuehl:

Last week, I received the brief report cited above from Dr. Kurt Snipes, Chief of the Cancer Surveillance & Research Branch at the California Cancer Registry (CCR). The study for this report was done at your request in response to concerns from Mothers for Retinoblastoma Awareness, a community group in the West San Fernando Valley. Because the authors of the report (who were not named) indicate that they consulted with me on their study, I am writing to voice my concerns with their work and to point out that I raised these concerns at the outset with the CCR staff and that I was not shown any data, findings, or text before the report was sent to your office. After highlighting their methods, results, and conclusions in the next paragraph, I will explain why I think the report is incomplete, what additional information should be provided, and how the authors' interpretation of their findings is potentially misleading.

To address the concerns of Mothers for Retinoblastoma Awareness, the CCR researchers compared the incidence rate of this cancer between 1988 and 2005 (an 18-year period) for children under age 5 who lived within approximately 10 miles of the Santa Susana Field Laboratory (SSFL) (the target population) to children of the same age, sex, and race/ethnicity distribution, who lived in California (the comparison population) during the same period. The target population was defined by a list of census tracts that were identified in an e-mail message sent to me by Dr. Margaret McCusker on July 13, 2007. The researchers identified 11 cases of retinoblastoma that occurred in the target population during the study period, and they estimated that 7.5 cases would be expected on the basis of observed rates in California as a whole. Because the 99% confidence interval (4.3 to 22.8) around the observed number included the expected number of 7.5, the authors concluded that "the incidence of retinoblastoma in the [target population] was not statistically significantly elevated." They further concluded that "[t]he relatively young age of the cases, and the high proportion of cases with bilateral disease, is suggestive of a genetic origin." The implication seems to be that retinoblastoma cases occurred randomly in the West Valley and that environmental factors had little or no effect on the risk of this cancer in the target population.

Given that this report was initiated in response to a community group that had identified 9 cases of retinoblastoma in their neighborhoods, it is important that the report include sufficient

documentation of their 11 cases to determine if they include those identified by the community group. Furthermore, they should have identified the general residential locations of cases and their dates of diagnosis on a map of the target region. Unfortunately, none of that information was provided. Not only did the census-tract map mentioned in the report (and sent separately to us) not have cancer cases or SSFL located, but it had no key to determine the meaning of the three colored lines surrounding SSFL. One might assume that the blue line (furthest from SSFL) represents the target region, but that does not appear to be the case. On the south, the blue line is only about 6 miles from SSFL, and it excludes several census tracts that were included in the list sent to me by Dr. McCusker and that included several cases identified by the community group.

In order to understand and make transparent to the reader the pattern of retinoblastoma incidence in the target region, I think the CCR report should include additional information in the form of a map of the region and a tabular summary of all cases of retinoblastoma diagnosed during the 18-year follow-up period. The authors should include in their report retinoblastoma cases that were diagnosed at ages 5+ during the 18-year period—though statistical analyses can still be restricted to cases under 5. The **map** should include the following features: a clear delineation of the target region showing all census tracts with their numbers; the scale of the map (i.e., number of miles per unit length); the location of SSFL and a circle showing a 10-mile radius around the facility; and the approximate locations of all cases, showing ID numbers (1-11) and date of diagnosis. The **table** should provide the following information for each retinoblastoma case: ID number, census-tract number, age and date of diagnosis, sex, race/ethnicity, and laterality (bilateral or unilateral). This information can be readily included in their report without providing patient identifiers that might raise confidentiality concerns.

A major limitation of their study is that the possible clustering of retinoblastoma cases in space and/or time is likely to be obscured by defining the target region so widely (about 314 square miles) and by making the follow-up period so long (18 years). If, indeed, there is a cluster of cases attributable in part to a common environmental exposure, it is very likely that its appearance would be substantially diluted using their approach. Despite this limitation, however, the CCR researchers still found that the incidence rate of retinoblastoma in the target population was $11/7.5 = 1.49$ times greater than the incidence rate in California as a whole (where 1.49 is an estimate of the incidence rate ratio). It should be noted that all 11 cases occurred during an 8-year period between 1998 and 2005; and, according to the community group, several cases occurred within a small sector of the target region. Of course, that latter information needs to be verified, but that cannot be done on the basis of data provided in CCR's report.

Another problem with the CCR researchers' methods is that they relied entirely on significance testing to interpret their findings—i.e., whether the p value for testing the null hypothesis of no difference in retinoblastoma rates between the target and comparison populations is less than 0.01 (called “significant”) or greater than 0.01 (called “nonsignificant”). Recognizing that clusters of disease occur by chance, the researchers applied a conservative criterion for statistical significance (instead of the more customary $p < 0.05$) in order to reduce the likelihood of a “false positive” result (i.e., concluding that there is an excess of retinoblastoma when there really isn't). It is important to recognize, however, that this “conservative” strategy also increases the likelihood of a “false negative” result (i.e., concluding that there is no excess of retinoblastoma when there really is one), which is contrary to the “precautionary principle” often applied in matters of public-health policy. Despite

finding that the incidence rate of retinoblastoma was nearly 50% greater in the target population than in California, the authors interpreted this result to be “not statistically significant” because the p value was greater than 0.01 (or equivalently, the 99% confidence interval around the rate ratio included one). Thus, they have prematurely interpreted their result as a chance finding. If this is a chance finding, I find it difficult to explain why no cases of retinoblastoma occurred during the first 10 years of the study period (1988-1997), but 11 cases occurred during the next 8 years (1998-2005). If we restrict the follow-up period to 8 years, 1998-2005, the incidence rate ratio, comparing the target population with California, is 3.19 (99% confidence interval = 1.20, 6.16). Applying the same criterion used by the CCR researchers, one would interpret this result to be “statistically significant.” Although I recognize the limitation of conducting such a *post hoc* test, it illustrates the problem of relying on significance testing to assess the possible clustering of retinoblastoma cases in a given region.

Aside from a p value greater than 0.01, the CCR researchers seem to dismiss the possible effect of environmental factors on retinoblastoma because 5 of the 11 cases were bilateral (affecting both eyes) and 5 cases were diagnosed before their first birthdays. Although this evidence does suggest that at least 5 cases were inherited in the sense that these children got a defective gene from a parent, it does not rule out the influence of environmental factors in causing these cases to occur. It is likely that the parents of most of these inherited cases did not have the same gene mutation as their children (the familial form of retinoblastoma), but that these cases arose from a new gene mutation that occurred in the germ cells of one of their parents. It is possible that these “sporadic heritable” cases occurred as a result of environmental exposures at the time of conception. Such associations between environmental exposures and this form of retinoblastoma have been reported by other investigators (e.g., Bunin et al. *Cancer Research* 1989; 49:5730-35).

In summary, I believe the CCR report is poorly documented, the findings are inappropriately interpreted, and the authors have not pointed out the limitations of their methods. The analysis conducted by the CCR researchers is a useful first step, but the findings should not be interpreted to mean that the observed cases of retinoblastoma were random occurrences or that they were not influenced by environmental factors. I realize that the CCR researchers do not have the data or resources to determine the causes of retinoblastoma occurrences in the West Valley, but I certainly hope they can provide the parents of these children with the information they deserve with an appropriate interpretation of their findings.

Sincerely,



Hal Morgenstern, Ph.D.
Professor and Chair

cc: Jeff and Cindy Mays