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September 27, 1983

M. S. DEAK
CPD

LOUISIANA CANCER POLICY

The response from both Du Pont and Conoco to your request for comments on the draft report entitled, "The Cancer Problem in Louisiana" has been strong and substantial. Conoco's comments are attached. Du Pont's are described below. Both sets of comments reveal a serious concern about the content of portions of the draft report. Taken together, the responses identify two major criticisms of the draft.

First, the draft's use of the word "epidemic" (see pages 1 and 25) to describe the incidence of cancer in Louisiana is inappropriate. "Epidemic" in this context implies that Louisiana's cancer rate is greater than that of the United States as a whole. Using Dr. Kardinal's own source of data (the American Cancer Society's 1983 Cancer Statistics), however, Louisiana's cancer death rate per 100,000 population is lower than the rate in 36 other states and is 10% lower than the national average.

Second, the draft sets forth a faulty syllogism (see pages 11-12 and 20) that cancer incidence is increasing, that the increase corresponds to the increasing production of synthetic organic chemicals, and that "occupational/environmental factors" are therefore probably to blame for much of the increasing rate of cancer assumed to exist. Dr. Pell points out the flaws in this analysis:

At the bottom of page 11, the paper [citing published articles by S. S. Epstein] states that "standardized cancer death rates show a progressive overall increase of 7% from 1935 to 1970 despite marked reduction in stomach cancer and cancer of the cervix (Table 14.)". First, the statement ignores the fact that the 7% increase includes lung cancer. When lung and other respiratory cancers are removed, the trend for non-respiratory cancers has been downward. 1 Second,

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Table 14 shows incidence rates (not death rates) that are taken from the three National Cancer Institutes' National Cancer Surveys done in 1937, 1947, and 1969-71. Incidence surveys require complete identification of all cancer cases occurring in a specific area. Reports must come from private physicians, clinics, hospitals, and death certificates. It is known that with each successive NCI cancer survey, the case-finding procedures were increasingly refined. As a result, some (or all) of the increased incidence may be due to improved case finding. For this reason, Doll and Peto preferred to use death rates to study trends, and preferably among people under 65 years. Their data on trends ² clearly show a predominance of declining trends.

Epstein's opinions and data are given more space than they deserve. They are presented uncritically, but warrant much criticism. His opinion that 20% or more of cancers are caused by occupational carcinogens is taken from the much criticized and discredited HEW "Estimates Paper." His opinion that lung cancer deaths have been increasing among nonsmokers has been effectively refuted by Doll and Peto. ³

In addition to these two fundamental criticisms, a number of other comments were directed to specific portions of the draft. They are summarized below.

Page 2, lines 8-10. For the sake of balance, the list of potential causes should include references to lifestyle factors (particularly smoking and diet).

Page 3, lines 1-2. Haskell doesn't believe that, on the basis of currently available evidence, one can conclude that cancer is a disease "with predictable behavior and probably of a specific etiology." This phrase should be deleted.

Page 3, lines 3-24. Again, for the sake of balance, an example of a lifestyle factor (probably smoking) should be inserted.

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- 1/ Doll and Peto, "The Causes of Cancer: Quantitative Estimates of Avoidable Risks of Cancer in the United States Today," Journal of the National Cancer Institute 1191, 1282-83 (1981).
 - 2/ Ibid. 1284-85.
 - 3/ Ibid. 1303-05.

Page 3, Statements 1-4 (bottom of the page). Neither Haskell nor Medical believes that these statements are valid. We would suggest the following language as a possible replacement:

1. Cancer is a disease that is still not well understood, but the pace of advancement in the scientific understanding of it has quickened in recent years.
2. Cancer appears to be a disease that can strike a variety of locations in the body yet shares some common characteristics.

Page 5, lines 11-13. According to IARC, the conclusions on these additional 18 carcinogens were derived from human and animal data, not "sufficient human data" alone.

Page 5, Statements 1 and 2. These statements seem stronger than justified by available scientific evidence. We would suggest the following rephrasing:

1. Most carcinogens seem to act by way of similar biologic processes in mammalian species that have been tested.
2. Substances that are carcinogenic in an animal species may be carcinogenic in other animal species, including man.

Page 5, Statement 4. The term "high probability" is ambiguous. If it means a 50% chance, statement 4 is probably okay. If, however, it means a 95% likelihood, then statement 4 is false.

Page 6, lines 16-17. We're not immediately familiar with the source of the 70,000 number.

Page 7, lines 4-22. The conclusion suggested by this section -- if mutagenic (in the Ames or another in vitro test) then ban it -- is inconsistent with current thinking. Perhaps the clearest indication of this inconsistency is contained in an article just published by Professor Ames himself:

Nature is not benign. It should be emphasized that no human diet can be entirely free of mutagens and carcinogens and that the foods mentioned are only representative examples. To identify a substance, whether natural or man-made, as a mutagen or a carcinogen, is just a first step. Beyond this, it is

necessary to consider the risks for alternative courses of action and to quantitate the approximate magnitude of the risk. . . . 4

Page 9, lines 26-29. These sentences belittle the contribution of Doll and Peto, whose 1981 paper written for the National Cancer Institute is the most authoritative epidemiological analysis of the relationship between cancer and exposure to chemicals available today. The sentence should be omitted and replaced with the following:

The proper response to such concern is additional research, however, not alarm. Doll and Peto, who placed the contribution to U.S. cancer mortality of occupational and environmental exposures to industrial chemicals at less than 5 percent (including 2 percent due to asbestos),* offered the following comments:

"The trends that are being recorded do not, however, suggest that the United States is beginning to experience an epidemic of cancer due to new factors. Indeed, were it not for the effects of tobacco, total U.S. death rates would be decreasing substantially more rapidly than they already are, and we are more encouraged by the benefits that are already being demonstrated from the control of known causes of cancer and other disease than we are dismayed by the appearance of new ones."**

4/ B. N. Ames, "Dietary Carcinogens and Anticarcinogens," Science, 221: 1256, 1261 (Sept. 23, 1983).

*/ Doll and Peto, "The Causes of Cancer: Quantitative Estimates of Avoidable Risk in the United States Today," Journal of The National Cancer Institute 1191, (1981); See Weistein, "Cost-Effective Priorities for Cancer Prevention," Science, 221:17 (July 1, 1983).

**/ Doll and Peto, supra at 1258-59.

Page 10, lines 11-15. Government should not simply give up its effort to encourage people to adopt a lifestyle that promotes health because the task is difficult. The principal lifestyle factors -- smoking and diet -- are important. As Doll and Peto noted, "[n]one of the other factors [in cancer incidence] can approach the importance of tobacco or the probable importance of diet." ⁵ Professor Weinstein suggested recently that governmental priorities should take account of the significance of these factors:

Epidemiologic insights should, however, lead us to examine the priority-setting problem in a broader framework. If industrial chemicals other than asbestos account for 3 percent of cancer deaths, the prospect of saving 12,000 lives each year (out of 400,000 cancer deaths) should encourage us to discover the key industrial agents and control exposure to them. But if 35 percent of cancer deaths are related to diet efforts to discover dietary factors in cancer might deserve an even greater claim on resources. ⁶

Page 12, lines 15-16. The 50x excess probably reflects the combined effect of asbestos and smoking, as Dr. Kardinal noted earlier in his draft (see page 6, lines 8-11).

Page 12, lines 17-20. As discussed above, we believe the estimates of Doll and Peto are more authoritative than those of Epstein.

Page 12, lines 24-25. The evidence for diet as a significant lifestyle factor is far stronger than indicated in the text. See, e.g., Ames supra n.4.

Page 13, lines 3-29. The reasoning leading Kardinal to the conclusion that "lack of industrialization" may help explain the lower cancer incidence in Utah is hard to follow. If non-Mormons have cancer rates higher than the general U.S. population, but Utah's overall cancer rate is relatively low, a more likely conclusion than Kardinal's would seem to be that the Mormon lifestyle is the principal cause of the low cancer mortality rate.

5/ Doll and Peto, supra, n.1, at 1258.

6/ Weinstein, M.C., "Cost-Effective Priorities for Cancer Prevention," Science, 221-17 (July 1, 1983).

Page 15, lines 18-28. Assessing and managing the risks posed by a carcinogen is, as Kardinal suggests, a difficult task. Unfortunately, that task is unavoidable in a world of limited resources.

Page 15, line 29 - Page 16, line 8. The question of whether there exist threshold levels of exposure to carcinogens is unresolved, but there is evidence suggestive of the existence of practical thresholds.⁷ Thus Kardinal's conclusory statement (see page 16, lines 3-5) that thresholds do not exist is not justified.

Page 16, line 10 - Page 25. This discussion of quantitative risk assessment (QRA) seems almost to have been an afterthought, and it's unclear exactly what it contributes to the paper. Nevertheless, if QRA is to be addressed in the draft paper, more than one reference should be used. A recent paper by Park and Snee ⁸ is an excellent discussion of QRA and should be consulted.

Page 25, Conclusion 1. For reasons discussed above, we would suggest deleting this conclusion and replacing it with the following:

1. Cancer is an important public health problem.

Page 25, Conclusion 4. We question whether the requisite scientific evidence exists to make this statement. We would suggest the following alternative:

1. The cause or causes of cancer are not yet well understood.

Page 25, Conclusion 5. We suggest expanding the sentence to read:

5. Progress in scientific research holds promise that cancer may be preventable in the future.

Page 26, Conclusion 14. For the reasons stated above, this conclusion is unfounded. It should be modified by merging it with Conclusion 15 to read:

14. Smoking and diet appear to make a significantly greater contribution to cancer incidence than other factors, including exposure to industrial chemicals, ionizing radiation, solar radiation, parasites, and immunologic factors.

^{7/} See, e.g., D. G. Hoel et al., "Implication of Nonlinear Kinetics on Risk Estimation in Carcinogenesis," Science, 219: 1032 (March 4, 1983).

^{8/} C. N. Park and R. D. Snee, "Quantitative Risk Assessment: State-of-the-Art for Carcinogenesis," in press.

Page 26, Conclusion 15. The text of the draft does not support this conclusion insofar as solar radiation is concerned. (Compare page 14, lines 25-26.) The conclusion should be merged as described above with #14.

Page 26, Conclusion 16. We suggest that Conclusion 16 be modified to read:

16. While levels of "acceptable risk" and risk/benefit ratios are difficult to formulate in the context of human exposure to potential carcinogens, there is no alternative in a world of limited resources.

Page 26, Conclusion 17. Human experience with formaldehyde (for example) suggests the existence of thresholds in humans. We suggest that Conclusion 17 be modified to read:

17. There is inadequate scientific evidence at present to determine conclusively whether safe thresholds for carcinogens may exist.


D. C. HOCHSTETLER

DCH:dwb

Attachment

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HASKELL LABORATORY

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Interoffice Communication

TO: Douglass C. Hochstetler
FROM: William K. Newbury
DATE: September 21, 1983
SUBJECT: Louisiana Cancer Policy

Outlined below are Conoco's comments on the draft of "The Cancer Problem in Louisiana" section of the report by the Governor's Task Force on Environmental Health.

We are extremely concerned with the draft because

- 1) it contains numerous technical inaccuracies and misstatements,
- 2) many of its conclusions are unsubstantiated by the text and,
- 3) the tone of the draft seems to suggest that regulation of industry is appropriate and justified despite the fact that no evidence is provided that industry is causing a problem or that regulation would reduce the problem if it were. In certain sections of the draft, Dr. Kardinal has presented a thoughtful, well-balanced review of the issues. However, we are as concerned as you that this draft must be modified substantially or we will find it being used to support the need for extensive new regulations in the state.

The Conoco Medical Division and Coordinating and Planning Department each reviewed Dr. Kardinal's draft. Both agree that the draft needs to be revised. Their specific comments are on Attachments I and II. Because of the short time frame for review, these comments represent our preliminary thoughts on the draft. The medical staff is gathering additional information to document our points. They have been in touch with Frank Bower and will coordinate their efforts with Haskell to avoid duplication of effort.

I will be in touch with you Monday to explore how we might best convey to Dr. Kardinal and the Task Force Staff the comments of Du Pont and Conoco.

William K. Newbury
W. K. Newbury

WKN:djb
Attachment

cc: W. K. Dietrich
J. L. Riddle
W. D. Rossiter
C. R. Wilhite

Attachment II

THE CANCER PROBLEM IN LOUISIANA

Comments From Conoco Coordinating and Planning Department

- Page #1 Not only the first sentence but the whole first paragraph should be removed. There is no context for the cancer figures cited in the paragraph. Without a comparison against earlier time periods or other states, the numbers have no value other than to scare people. The second paragraph is really the appropriate introduction because it stresses the complexity of the issue and the need for careful scientific analysis.
- Page #9 The second paragraph under "Cancer and the Environment" should be taken out entirely. The author doesn't even define the two categories until page 10, and already he is addressing industrial-caused cancers. This leaves the impression that "environmental factors" is just another name for industrial-caused cancers. In addition, the last sentence is totally illogical. Dr. Higginson has acknowledged that his original 90% estimate is too high. However, this is no reason to conclude that Doll and Peto's 5% figure may be too low.
- Page #10 The second paragraph is a dangerous one because it could influence the recommendations that will be made by the Task Force. Some, who want to achieve the "baseline" level recommended on page 14, may use the argument that individual behavior is so difficult to change (as an excuse) to justify ratcheting down extra hard on industry. The paragraph must make it clear that administrative ease alone is not sufficient criteria for state action. Just because government regulation of environmental factors may be "easier" does not make it right to focus on those factors and ignore life-style. Action must focus on solving the real causes of the problem not just something that's easy to regulate.
- In the Life-style and General Environment sections, Dr. Kardinal relies on only one source in each section. The discussion would be much more convincing if he referenced other sources as well. The 9/23/83 Science article on dietary carcinogens should be discussed in some detail in this section.
- Page #11 The last sentence of the Life-style section is totally misleading. Doll and Peto provide very clear estimates of the relative role of life-style and environmental factors.
- Page #12 Table 14 contains a number of serious errors in its calculations and, moreover, fails to address the basic conclusion of the data. A careful analysis of the data

suggests a totally different conclusion than the one stated in the text. The table's Net Change column was developed by simply adding the numbers in the other two columns. This is wrong for two reasons. The 1947-69 column encompasses 22 years whereas the 1937-47 column covers only 10 years. The changes in the former should be given twice the weight. Second, percent changes in the 1947-69 period start in almost every case from a higher base than in the 1937-47 period. Thus, the absolute change in the 1947-69 period will be larger than a similar percent change in the 1937-47 period. Even with its faulty analysis, the table's data still make a very important point. The rate of increase for 1947-69 has either slowed or turned negatives in two-thirds of the categories. Of the ten cancer types, only lung cancer is increasing among all individuals. If you ignore this category, which everyone agrees is a problem, the proportioned improvement is even greater. Based on these conclusions, the flat statement of "a progressive overall increase of 7%" is totally unjustified.

- Page #12 The second full sentence should be removed for two reasons. The Task Force is charged with looking at exposure problems today. It is not going to do anything to correct possible exposure in the past. Second, the sentence implicates synthetic organic chemicals as a cancer cause simply by indicating the coincidental time frame for the growth of the industry and normal latency periods. No evidence is provided that there is any causal relationship. The statement is pure speculation.
- Page #13 The last sentence in paragraph 3 must be removed. Having spent a page of text making the case that the Mormon life-style is directly correlated with low cancer rates in Utah and making no mention of industrialization, the author has absolutely no basis for his concluding sentence that the lack of industrialization may be a more important reason than life-style for the state's low cancer rate.
- Page #19, The lengthy quotation from the National Cancer Advisory Board's draft policy on risk assessment includes substantial material that is not relevant to a discussion of the cancer problem in Louisiana. That material, which includes the Models, Regulatory vs. Scientific Issues, and Who Should Do It sections, should be dropped out.
- Page #22 The first full paragraph, which stresses the current lack of understanding concerning interspecies variations and the uncertainty inherent in animal to man extrapolations, sharply contradicts the numbered statements at the bottom of page 5.

Summary Statements

1. As mentioned earlier, this statement should be removed.
13. Experts would agree that life-style is, not just appears to be, a major cause of cancer in the U.S.
14. The statement is misleading because the author does not indicate what he includes as occupational and environmental factors. Even with a very broad definition, there is very little scientific evidence to back up the assertion.
16. This statement is at best misleading. Defining acceptable risk and risk/benefit ratios is by no means impossible. Selecting the best one for each situation is a difficult value choice but not impossible.

The Cancer Problem in Louisiana
prepared for the Governor's Task Force
by Carl G. Kardinal, M.D.

Comments from Conoco Medical Division

Page 2

2. The first sentence is clearly inflammatory with no comparison data provided.
3. Self-contradiction in last sentence of second paragraph stating many of the chemicals are "carcinogenic in animal systems and most of which have never been tested for carcinogens in animals or humans."

Numbered items at the bottom of the page:

1. The cause of cancer is unknown and, contrary to the statement, it may strike anyone, anywhere at anytime.
 2. While cancer is not an "inevitable" part of the aging process, the risk of cancer increases with age.
 4. Absolutely no evidence that each type of cancer has its own specific cause
 5. Based upon unfounded assumptions listed in item 4
 6. All problems in life are "potentially" solvable or preventable.
4. Other causes of cancer should be addressed here in the same arena as the possible chemicals agents, not ten pages later where effect is minimized.

Last paragraph is theoretical and concepts apply to only initiators, not to promoters. Does not account for known repair mechanisms nor immunological mechanisms.

5. In paragraph two, Dr. Kardinal can cite only 36 chemicals listed by IARC as "known" or "probable" carcinogens. This directly contradicts his earlier statements of page three that of thousands, many are carcinogenic.

Numbered items at bottom of page:

1. There is no evidence to support this statement.
2. What is the evidence to substantiate this statement?
Can Du Pont (Haskell) check references to see who drew this conclusion?
4. False logic to assume truth of converse from premise of item 3. Requires qualitative and quantitative risk assessment before such a conclusion.

Page 8

Cost is several hundred thousand not just several thousand.

Question validity of statement "However, data are generally highly reliable and reproducible."

(W. D. Broddle, Ph.D., should provide examples to refute this claim.)

The Ames Test cannot assess relative risk.

7. This is no substantiating evidence for false logic that because carcinogens are mutagens that all mutagens are carcinogens. In fact, the last sentence in the paragraph clearly states that the premise that all carcinogens are mutagens is a false premise.

8. Section on Geographic Studies makes no real point. It is obviously devised to overwhelm or confuse. The statement regarding persistent high rates of stomach cancer in migrant Japanese implying the criticality of early life exposure ignores the continuation of dietary habits.

9. Higgenson is misinterpreted here by implication and has refuted the implication that occupational and environmental are synonymous.

The last sentence is not supportable by the evidence.

10. When cigarette related cancers are accounted for, the cancer rate is decreasing.

The first paragraph misleads by trying to isolate lifestyle factors from environmental factors.

12. The Mormons' occupational exposures, etc. would be virtually the same as other population segments. Thus Dr. Kardinal's own evidence would substantiate lifestyle/dietary habits as the major factor.

12. The 19% and 22% quoted in line 3 are not adjusted for longevity.

The evidence is that voluntary and involuntary smoking accounts for any increase in cancer rates. The second sentence of paragraph two implies environmental and occupational are synonymous which is false. The last sentence of paragraph two should read ----- asbestos workers who are smokers -----.

The third paragraph draws a conclusion based upon only one cited reference (Epstein and Swartz) and totally ignores all other evidence.

Page 6

14. We can agree with the recommended baseline which is basis to recommend smoking cessation program not for more regulation of occupational condition. (re: comments about page 12).

Dr. Kardinal offers no evidence to support his claim that the impact of the other potential causes of cancer is secondary.

In his discussion of immunological factors, Dr. Kardinal totally ignores their role in cancer prevention as opposed to simply discussing etiology.

The last sentence under Immunological Factors is a subjective conclusion that is unsubstantiated and contrary to evidence.

The role of immunological factors has been well documented as part of the individuals defense against cancer.

Dr. Kardinal avoids the discussion of immunological control factors in the consideration of familial pre-disposition. Inbreeding can suppress these immunological factors reducing natural defenses.

15. Viruses are known to exist that will cause cancer when administered to rats, mice, and other laboratory animals.

The evidence that viruses are carcinogenic is as strong as the evidence against chemicals. (We should compile and cite references.)

The first paragraph discussing Risk Assessment is purely an emotional appeal to arouse regulatory fervor.

The second paragraph uses statistical probability to infer that every individual exposed to a chemical will develop cancer.

16. The first sentence of the first whole paragraph is a false statement. There are numerous animal studies demonstrating "no-effect" levels. (W. D. Broddle, Ph.D., should provide documentation.)

- 19-25 Dr. Kardinal points out problems of extrapolation from extreme high dosages of laboratory toxicology studies to extremely low dosages in occupational exposures. This should be emphasized. The effect of the Howitzer extrapolated to the BD makes risk assessment extremely suspect.

Toxicological studies dose animals until an effect is obtained! Extrapolation from such work has to be extremely questionable, especially extended beyond toxicological effect into risk assessment.

Summary

- 1.6. — These points have already been addressed.
7. Simplistic and theoretical statement which has not been proven true.
- 8.
10. These points have already been addressed in our responses.
- 12.
14. This statement is not true.
- a. There is no evidence that occupational factors have in any way increased the cancer role.
 - b. Environment includes lifestyle factors.
 - d. In fact, the incidence of cancer is decreasing not increasing.

Tables 11 and 12

These data should support argument of lifestyle as major factors since Japan is an industrialized nation.