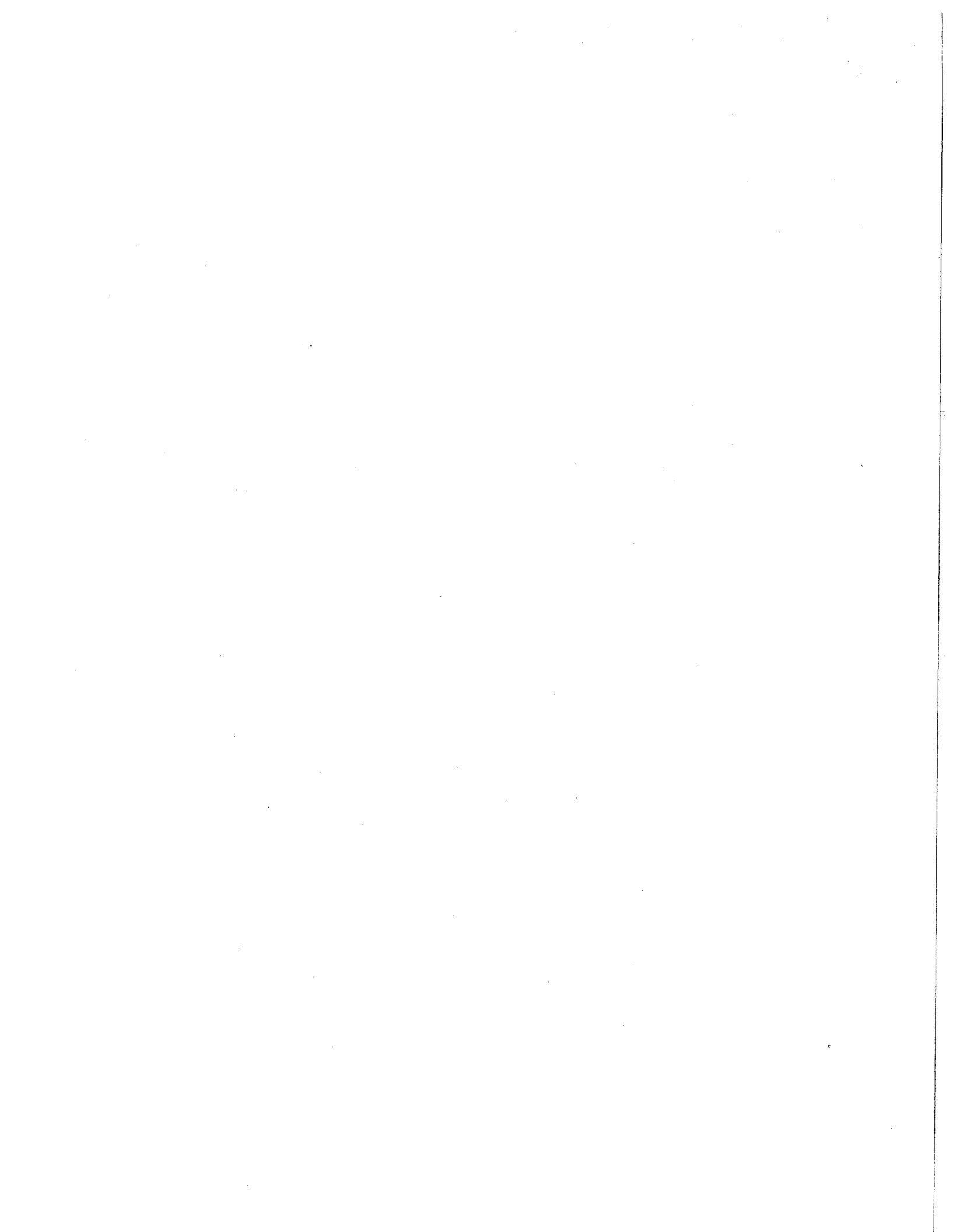


**GUIDANCE CRITERIA FOR IDENTIFYING CHEMICALS FOR LISTING AS
"KNOWN TO THE STATE TO CAUSE CANCER"**

1. General Principles

- A. The criteria included herein shall be utilized by the Office of Environmental Health Hazard Assessment Science Advisory Board Carcinogen Identification Committee (CIC) to identify those chemicals which are to be recommended for listing as known to the State to cause cancer. This listing is for purposes of fulfilling the mandate of the Safe Drinking Water and Toxic Enforcement Act of 1986 ("Proposition 65").
- B. These criteria are intended to give the CIC maximal flexibility in evaluating all pertinent scientific information in determining whether a chemical is known to the State to cause cancer. They are intended neither to limit the scope of the Committee's consideration of all appropriate cumulated scientific information, nor to limit the use of best scientific judgement available at the time.
- C. In evaluating the sufficiency of available data, a "weight-of evidence" approach shall be used to evaluate the body of information available for any given chemical. The body of evidence shall include all evidence bearing on the issue of carcinogenicity shown through scientifically valid testing according to generally accepted principles.
- D. The Safe Drinking Water and Toxic Enforcement Act of 1986 states that a chemical is known to cause cancer "if in the opinion of the state's qualified experts it has been clearly shown through scientifically valid testing according to generally accepted principles to cause cancer" without further restriction. Thus if the weight of scientific evidence clearly shows that a certain chemical causes invasive cancer in humans, or that it causes invasive cancer in animals (unless the mechanism of action has been shown not to be relevant to humans), the committee will normally identify that chemical for listing.
- E. The application of causation criteria requires scientific judgements which can only be based on experience, not only with the interpretation of epidemiological studies or animal carcinogenicity experiments in general, but with the circumstances of exposure, the physical and demographic setting, the nature of classification, including pertinent clinical and histologic schemata, and the qualifications of the investigator. Thus, few of the criteria are amenable to the use of absolute restrictions of either a quantitative or qualitative nature.
- F. Whether evaluating the evidence for carcinogenicity in animals or humans, CIC members may make judgements utilizing other, more indirect, scientifically valid observations obtained using generally accepted methods and principles. Such information may derive from studies of genetic toxicology or DNA repair using in vitro methods, cultured mammalian cells, or living prokaryotes, lower eukaryotes, plants, or insects, although changes induced in whole mammals must be considered more pertinent. Quantitative variations in mutagenicity or other short term phenomena cannot be presumed to always



parallel quantitative variations in carcinogenicity, since not all carcinogens are mutagens. Taken alone, a negative test can rarely offer strong evidence against carcinogenicity; although well conducted negative studies can provide important contributory evidence. Each of the following categories of knowledge may be pertinent to carcinogen determinations.

- Physical and chemical characteristics of the chemical
- Absorption, distribution, metabolism, and excretion characteristics of the chemical
- Structure-function and structure-activity relationships
- Organ-specific and systemic toxicity, whether after short or long latency
- Protein binding, and cellular receptors
- Formation of DNA-adducts by means of chemical binding
- DNA repair processes
- Effects upon the methylation status of DNA
- Mutagenicity of the chemical and its propensity to cause chromosomal damage
- Mutational spectra in observed tumors with known links to environmental chemicals
- A capacity to produce benign tumors known to progress to malignancy
- A capacity to produce other effects known to be pre-neoplastic

Epidemiological and experimental studies of such surrogate outcomes must be held to the same strict criteria as studies of invasive cancer.

2. Generally accepted principles of scientifically valid studies of carcinogenesis.

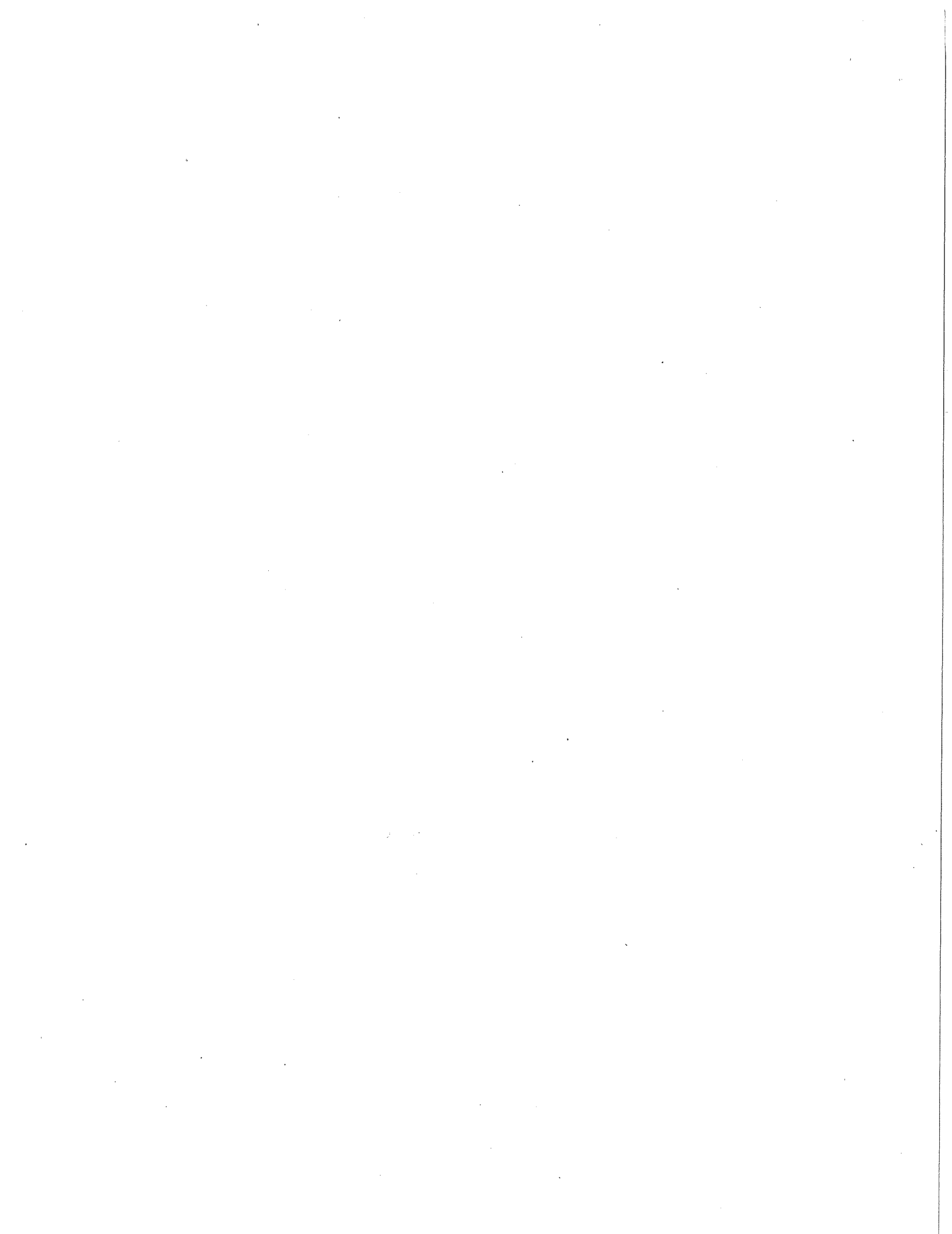
A. Epidemiological studies of carcinogenesis in humans will be interpreted as showing a causal relationship between the exposure and the cancer outcome depending on the weight of evidence.

i) Interpretation of the evidence is greatly facilitated by the availability of the specific details of pertinent studies. These details would include:

- a) The setting and the nature of the population studied
- b) The study design and the sequence of observations
- c) The operational definitions of exposure and tumor outcome
- d) The means of controlling pertinent bias and confounding
- e) The sample size(s) and the details of the analysis, including statistical testing

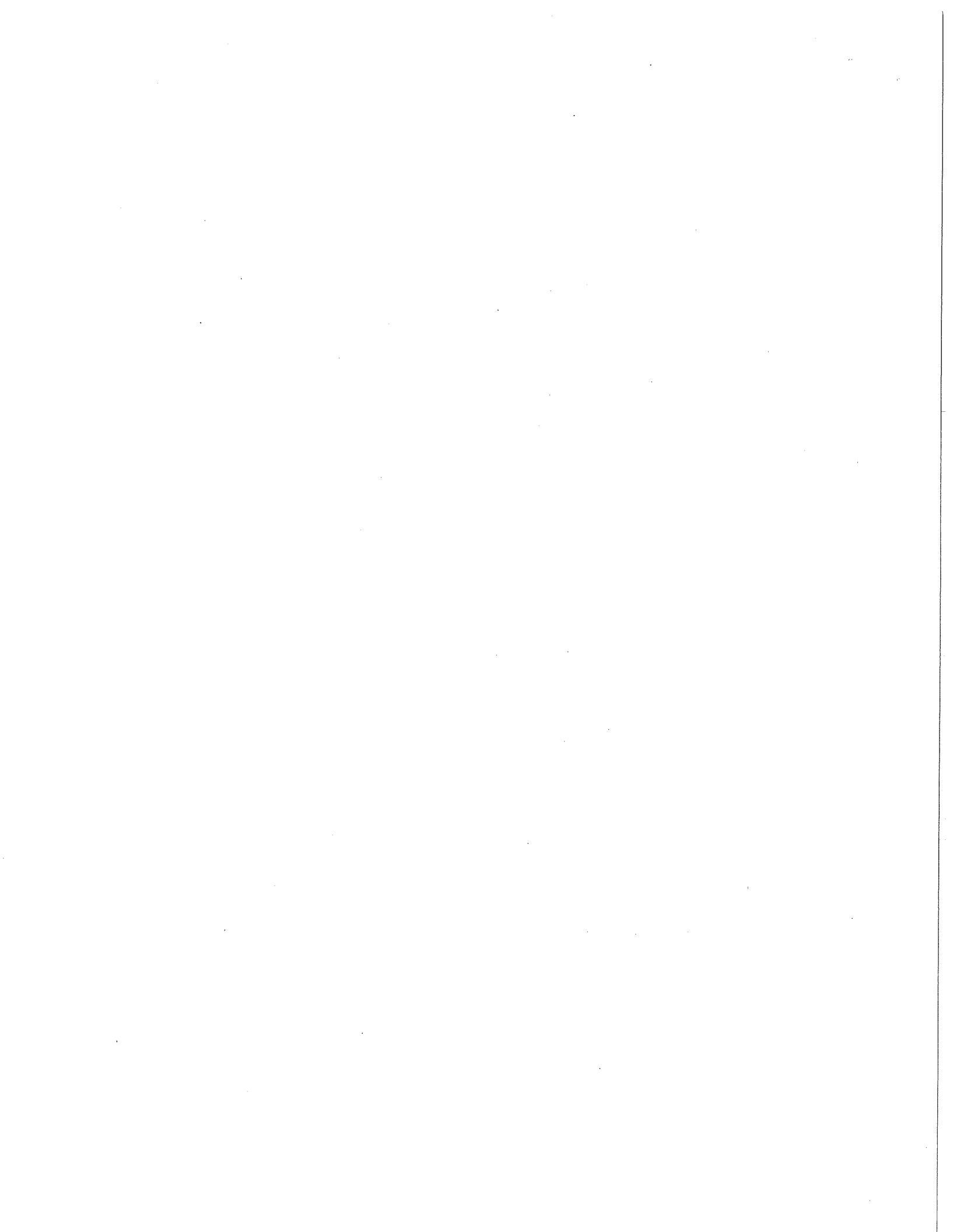
ii) The weight of evidence depends upon the degree to which each of the following propositions can be verified or rejected.

- a) The occurrence of the exposure and the occurrence of the cancer are associated, such that the outcome is shown to appear more frequently among the exposed than among the unexposed.
- b) The observed association cannot be reasonably explained by chance, based on conventional statistical criteria interpreted in the context of the number of comparisons made.
- c) The observed association is unlikely to be due to any link between the exposure and other known or presumed determinants or well-understood predictors of the outcome. The existence of such other known or presumed determinants does not, by itself, provide evidence for or against a finding of



carcinogenicity. This criterion can ordinarily not be fulfilled by observations that link the characteristics of groups rather than those of individuals.

- d) The observed association is unlikely to be explained by biased working definitions of the exposure or the cancer, or by biased methods of enumerating either of them.
- e) The plausibility of causation is undiminished or is enhanced by the detailed characteristics of the observed association as follows; none of these individual characteristics provides an absolute criterion for or against causality by itself.
 - 1) The strength of any positive association observed. Credibility is enhanced to the degree that the risk ratio rises, especially (arbitrarily), above 1.5.
 - 2) The relationship between the dose and/or the duration of the exposure and the strength of the association. In general, a direct relationship between these two quantities enhances the plausibility of a causal explanation.
 - 3) Causality of the observed association is consistent with what is known of the toxicological and physiologic effects of the exposure, and with the known causation and pathogenesis of the cancer in question.
 - 4) The consistency and brevity of the latent period between exposure and the time of appearance or diagnosis of malignancy.
 - 5) The histological and anatomical description of the tumors occurring after exposure, including their degree of malignancy or malignant potential.
 - 6) The biologic credibility of causation as an explanation for the pattern of time intervals between the period of exposure and the appearance of the cancer. In general, statistical variation around a specific period of latency enhances the plausibility of a causal explanation.
 - 7) The existence of multiple studies, i.e. multiple independent observations of the same relationship, each of which fulfills the above criteria. These are especially compelling if studies differ in respect to study design, population or setting, measurement technology, analytic strategy, time frame, or means of estimating what would be expected under the hypothesis of no association.
 - 8) The absence of any unambiguous observations which are truly inconsistent with the existence of a causal association. To be informative, a negative study must be of such quality that, if positive, it would have added to the weight of evidence. Such results should be based on definitions of exposure and cancer outcome which are valid and at least as sensitive and specific (i.e. have at least as high positive and negative predictive values) as studies in which an association has been (or would



be) observed. The existence of strong and diverse indirect evidences such as are listed under General Principle F above.

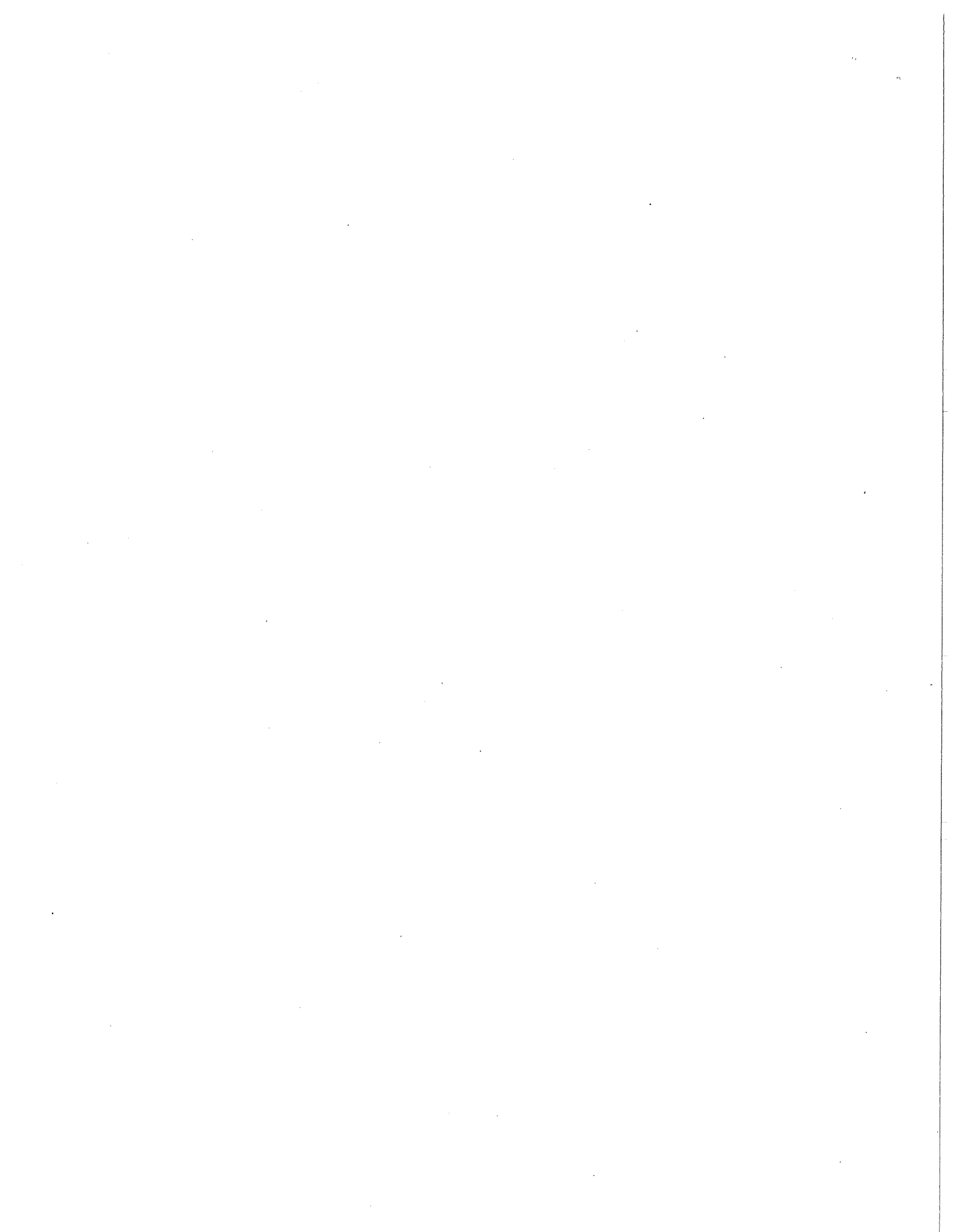
B. Studies of carcinogenesis in animals will be interpreted as showing a causal relationship between the exposure and the cancer outcome depending on the weight of evidence deriving from studies employing scientifically valid principles of testing.

i) Interpretation of the evidence from animal studies is greatly facilitated by the availability of the specific details of pertinent studies. These details would include:

- a) The clear definition and, if a single substance, the high purity of the agent under test. If pertinent, the means by which it was collected or extracted, stored, and delivered. In the case of mixtures, the detailed characterization and composition of the sample.
- b) The route, schedule, and dosage of exposure and the duration of follow-up. How the dose was monitored, especially in the case of inhalation experiments.
- c) The magnitude of the test dose relative to the maximum tolerated dose.
- d) The species, strain, sex, and age of the experimental animals.
- e) The fact and method of animal selection and randomization, if any.
- f) The number of animals in the exposed and in the control groups.
- g) The duration of follow-up, the proportion of surviving animals at risk, and the criteria by which the experiment is terminated.
- h) The histological and anatomical description of the tumors occurring in both exposed and control animals, including the degree of malignancy or malignant potential of the tumors.
- i) The timing of the appearance of tumors.
- j) The method of analysis, considering any necessary adjustments for differential survival, differential examination, historical as well as concurrent control experience, and the distinction between progressive tumors and non-progressive tumors found at autopsy.

ii) The weight of evidence depends upon the degree to which each of the following propositions can be verified or rejected with respect to malignancies or tumors of malignant potential.

- a) Tumors are found to occur in excess after exposure to the agent.
- b) Tumors appear more frequently in the exposed animals than in the unexposed comparison group.
- c) The observed difference cannot be reasonably explained by chance, based on conventional statistical criteria interpreted in the context of the number of comparisons made.
- d) The frequency of the unexpected tumors is related to the dose of the agent.
- e) The plausibility of causation is undiminished or is even enhanced by the detailed characteristics of the observed association as follows; none of these individual characteristics provides an absolute criterion of causality by itself.
 - 1) The higher the ratio of tumors in exposed to tumors in control animals, the more compelling the result, implying that unusual

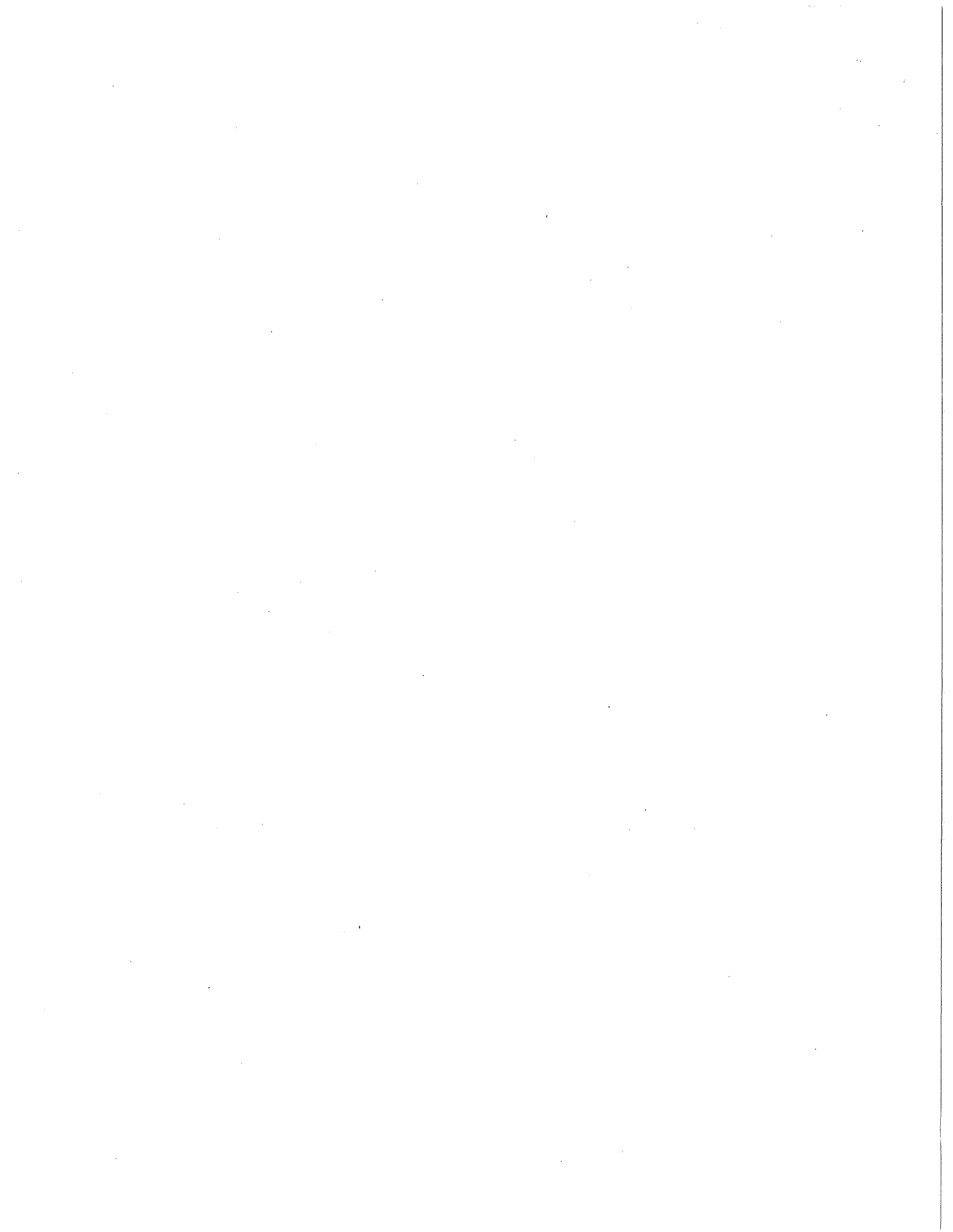


tumors, occurring in sites rarely affected under ordinary circumstances, are of special interest.

- 2) The tumors produced are more aggressive than those occurring in the absence of exposure. If benign, the tumors are of a type known to progress to malignancy.
- 3) Tumors are produced at an especially low dosage of exposure.
- 4) Tumors occur in unusual variety, or are produced at an unusually young age or after an especially short interval.
- 5) Tumors have been found to occur in significant excess (in order of increasing significance) in the two genders of a species, in two distinct species, or in two different experiments carried out in two different laboratories under different protocols. The following circumstances may constitute exceptions to this rule:

-- A single study in one species might be considered to provide sufficient evidence of carcinogenicity, if the malignant tumors occurred to an unusual degree with respect to frequency, type, location, age at onset, or low dosage, or in a strain not otherwise prone to such tumors.

-- Evidence of carcinogenicity in animals deriving from a single study or from multiple studies incompletely or inconsistently described might be considered sufficient if heavily supported by the indirect evidences described under General Principle F above.





Office of Environmental Health Hazard Assessment

Proposition 65 - Policy and Procedure documents

Availability of the Final Guidance Criteria for Identifying Chemicals for Listing as "Known to the State to Cause Cancer"

[03/05/2001]

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