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DATE: March 31, 2005

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ATTENTION: Ms. Georgi A. Jones, Hana Pohl, M.D., Ph.D., Ms. Yulandia Jordan

Dear Ms. Jones, Dr. Pohl, and Ms. Jordan:

These comments respond to a *Federal Register* notice (call for comments) by the Agency for Toxic Substances and Disease Registry (ATSDR) in the Department of Health and Human Services [*Federal Register 69(245):* 76768-76769 (December 22, 2004)], designated [ATSDR-202]. The comments primarily relate to the notice of availability of a "Guidance Manual for the Assessment of Joint Toxic Action of Chemical Mixtures."

The notice did not explain where to send (or who would receive) these comments. Therefore,

Consultants in Toxicology, Risk Assessment and Product Safety (CTRAPS), which is a small business in McLean, VA and which conducts biomedical research, is sending these comments to the following three persons referenced in the notice: Ms. Georgi Jones, Director of the Office of Policy, Planning, and Evaluation in National Center for Environmental Health and ATSDR, Dr. Hana Pohl in ATSDR's Division of Toxicology, and Ms. Yulandia Jordan in ATSDR's Office of Communication.

Some of CTRAPS's biomedical research involves the assessment of toxic effects of chemical substances in the environment and in mixtures. In addition, CTRAPS scientists have commented to Federal Agencies about mixtures, including mixtures of dioxins, the major example of substances in ATSDR's mixtures approach (Wilson, 1987; Charnley and Wilson, 1991; Byrd, 1995; Byrd *et al.*, 1995a; Byrd *et al.*, 1995b; Byrd *et al.*, 1998). So, CTRAPS has vital interests in the assessment of toxic effects of mixtures of chemical substances and Federal risk characterization practices.

SUMMARY: For reasons explained in detail (below), CTRAPS recommends that ATSDR withdraw its mixtures approach and propose it through the normal notice and comment process of informal rule making. Some of CTRAPS's reasons are as follows: (a) ATSDR's direct promulgation of a final version of its mixtures approach, in the form of a Guidance Manual, lacks a rationale to forego the informal rule making procedures of proposal and comment that the Administrative Procedures Act requires. (b) ATSDR's mixtures approach is based on subjective, not objective criteria. This mixtures approach asks ATSDR personnel to assign values to substances in mixtures. These values have structural relationships to substances with known biological activities, not values based on empirical bioassay. Inherently, ATSDR calculates the toxicity of a mixture, using assigned values for the constituents of the mixture. Subjectively assigned values mean that the assessment of "toxicity" in a mixture is a subjective process. In addition, ATSDR's mixtures approach uses numerical values to represent subjective estimates of expected "toxicity" for different substances. Both the numerical values and the mathematical processing of the numerical values, obfuscate ATSDR's mixtures approach. The numerical values and mathematical procedures give a false impression of precision to the approach. (c) ATSDR could, but did not, properly use experts' subjective assessments to decide which mixtures merit empirical assessment. (d) ATSDR needs a stopping point, beyond which experimental evaluation of a mixture will have no value, or some other way to set priorities on research needs. (e) The nature, direction and magnitude of a biological interaction, if any, between substances in a mixture will remain uncertain until ATSDR develops an evaluation process based on experimental evidence.

INTRODUCTION: These comments respond to a *Federal Register* notice (call for comments) by the Agency for Toxic Substances and Disease Registry (ATSDR), Department of Health and Human Services [*Federal Register 69(245):* 76768-76769 (December 22, 2004)], designated as [ATSDR-202] and to more general policy aspects, including ATSDR's "draft Guidance Manual for the Assessment of Joint Toxic Action of Chemical Mixtures."

DETAILED COMMENTS:

(A) ATSDR's notice lacks a rationale for either promulgation of a direct final rule or disguising a rule as a guidance document. ATSDR's notice of availability is equivalent to a direct final rule for ATSDR's mixtures approach, because an understanding of the accompanying interaction profiles is impossible without the amended Guidance Manual. CTRAPS would have appreciated an opportunity to comment, as a member of the public, on ATSDR's mixtures approach.

CTRAPS is not automatically opposed to the promulgation of direct final rules. However, an agency should provide some kind of justification for the necessity of bypassing normal notice and comment procedures (DeLong, 1989). The *Federal Register* notice [*69(245):* 76768-76769 (December 22, 2004)], titled "Notice of Availability of a Guidance Manual for the Assessment of Joint Toxic Action of Chemical Mixtures and Nine Interaction Profiles CD-ROM [Final Documents] and Two Interaction Profiles [Drafts for Public Comments]," calls for comments, but ATSDR formally requested comments only on the two interaction profiles. ATSDR's notice did not call for comments on either the overarching elements of its mixtures approach or the Guidance Manual. In substitution, the Guidance Manual apparently underwent peer review and an Agency-wide review. Neither process was transparent, nor were these processes open to the public. Neither process can substitute for public notice and comment.

CTRAPS, the organization responding to this notice, commented on one of the two interaction profiles in a separate document. However, CTRAPS also doubts the propriety of a direct final rule, which contains policies hidden within a guidance document and which is necessary to understand an interaction profile. The comments below show that CTRAPS objects to some aspects of ATSDR's mixtures approach. Overall, CTRAPS recommends that ATSDR review the notice in the light of the requirements of informal rule making, withdraw its mixtures approach, formulate it as a rule, propose it, and accept comments on it.

Similarly, CTRAPS does not instantly oppose the development and distribution of guidance documents or guidelines by Federal Agencies without public notice and comment. CTRAPS is not aware of any necessity for an agency to engage in informal rule making procedures to develop a guidance document. Ostensibly, any agency can provide guidance to its own employees about operations under ideal circumstances without engaging in a rule making. However, CTRAPS is not aware of any harm that will come to an agency that notifies the public about its policies and accepts comments on the proposed policies. The process of promulgating guidance does not entitle an agency to impose new requirements on the public without engaging in informal rule making (no stealth rule making).

(B) Some scientists will object to ATSDR's mixtures approach, because it improperly uses subjective speculations about the toxicity of mixtures, not experimental determinations, and because its unnecessary numerical procedure conceals a lack of precision.

(1) ATSDR's mixtures approach uses a weight of the evidence procedure to assign numerical values to substances in a mixture, based on opinions about structural relationships of a substance to other substances with known biological activities in mixtures. Inherently, the idea that a Federal agency can calculate the toxicity of a mixture, using assigned values for the constituents of the mixture, makes the assessment of "toxicity" of a substance in a mixture an uncertain, subjective matter. ATSDR's mixtures approach assumes that each substance in a mixture functions in isolation from other substances, such that joint toxicological activity can be estimated by summation, until a sufficiently high concentration is reached, when an interaction (antagonism or synergy) occurs. CTRAPS disagrees that ATSDR's mixtures approach can predict (a) the necessary concentration to achieve a departure from isolated function of components of a mixture, (b) the direction of departure from additive values, or (c) the magnitudes of departures at different concentrations. No basis for assigning values to substances, except for an empirical evaluation through bioassays, is "scientific."

(2) ATSDR's speculations about the properties of substances in mixtures lack theoretical justification. Little test data support the assumptions underlying ATSDR's mixtures approach. Minimally, a more comprehensive and understandable mixtures approach would describe mixtures, name example substances, and cite their bioassays. Instead, ATSDR assumes the capacity to assign values to substances, based on structural relationships to other substances with known biological activities. Such assignments can fail in theory because of differences in the following:

> **(a) Metabolism:** ATSDR assumes that substances with similar modes of action will exhibit predictable additive responses at known exposures. However, the scientific literature contradicts this assumption (Borgert *et al.*, 2004). In several instances and in theory, differences in metabolism will yield unpredictable responses from structurally similar substances. ATSDR's mixtures approach assumes that two structurally similar substances undergo a similar metabolism.
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> **(b) Selectivity for one of several biological activities:** A prototypical substance may have several biological activities. In theory, a structurally related but different substance, might interact with the prototype in proportion to concentration throughout the response range, but may lack, even inhibit, one or more of the other biological activities of the prototype. The substance in question also may possess another biological activity, not seen with the prototype. ATSDR's mixtures approach assumes that two structurally similar substances will possess all of the same biological activities and these activities only (Safe *et al.*, 2000).
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> **(c) Partial agonist activity:** The prototypical examples of applications of

the assumptions contained in ATSDR's mixtures approach are two classes of chemical substances: dioxins and permethrins. Both classes contain structurally similar substances with similar biological activities, including alleged carcinogenic activity, and similar modes of action. Federal Agencies assume that dose-response relationships for carcinogens will have no threshold and exhibit proportionality of exposure to biological outcomes (OSTP, 1985; EPA, 1986; Wilson, 1996). This property makes evaluation of the risk of mixtures containing dioxins or permethrins a simple, if potentially unrealistic, matter.

A.J. Clark (1933) showed that typical equilibrium data between drug concentrations (or doses) and the magnitude of biological effect coincided with the hyperbolic relationship expected for the formation of a drug-receptor complex according to the law of mass action. Experiments with hormones and drugs confirmed Clark's idea. The development of classical receptor theory culminated in work by E.J. Ariens (1954, 1964), who expanded the theory and created a symbolic system to manipulate its findings. This system requires two numbers to characterize each substance, not one, as ATSDR's mixtures approach assumes.

Ariens also contributed the concept of intrinsic activity to the classical theory. Some substances apparently bind to a receptor fully, yet they elicit only a part of the maximum biological activity. In Ariens' view these "partial agonists" had some, but reduced intrinsic activity in comparison to a "full agonist" (usually the parent drug or a hormone to which the partial agonist was compared).

Both Clark and Ariens made use of a simple assumption that receptor occupancy was proportional to the percent of maximum effect. This assumption enabled presentation of their ideas and derivation of equations. However, neither pharmacologist believed that these assumptions held for most biological systems. Clark stated that proportionality seemed too simplistic a concept. Ariens explained that direct proportionality between **[LR]** complex and effect was a simple case of a larger, more likely set of circumstances.

According to the law of mass action, at equilibrium the rate of formation of a substance-receptor complex is the same as the rate of dissociation. The rate of forward reaction is proportional to the concentrations of uncomplexed substance and receptor. Using common chemical kinetic notation, where $\mathbf{k_i}$ is the kinetic rate coefficient, the rate of the forward reaction is proportional to the concentrations of uncomplexed substance and receptor ([L] and [R]),

$$\mathbf{V_{forward} = k_1[L][R]}.$$

The rate of reverse reaction is proportional to the concentration of complex ([LR])

$$\mathbf{V_{backward} = k_2[LR].}$$

At equilibrium, the forward and backward rates are equal, and thus:

$$\mathbf{k_1[L][R] = k_2[LR].}$$

The equilibrium constant for dissociation of the complex, **K**, is thus equal to the ratio of the kinetic rate coefficients:

$$\mathbf{K_{equilibrium} \quad \frac{k_2}{} = \frac{[L][R]}{[LR]} \qquad k_1}$$

In receptor kinetics a change in external conditions changes the concentration of the substance near the receptor rapidly. K is an apparent dissociation constant. For some pharmacologically active substances, data about the concentrations of receptors and substances do not exist. Instead, pharmacologists estimate dissociation constants from applied concentrations, delivered doses, or other exposure data.

Pharmacologists often measure apparent affinity and equilibrium binding constants, even lacking biochemical knowledge about the receptor(s) involved, by measuring exposure-response relationships. Such empirical exposure-response relationships depend on both pharmacokinetic and mode of action processes. Experimental phenomena, which classical receptor theory could not explain, led to a general receptor theory. Classical receptor theory made two assumptions that general receptor theory does not, as follows:

- Biological activity is directly proportional to the concentration of receptor complex with a substance.
- Maximum biological activity occurs when the substance occupies all receptors.

Nickerson and Stephenson independently showed that less than full receptor occupation could achieve a maximum biological effect (Nickerson, 1956; Stephenson, 1956). Each advanced the idea that excess receptor capacity was a general state. Stephenson proposed modifying classical receptor theory by introducing two different assumptions, as follows:

- A substance can produce $\mathbf{E_{max}}$ without occupying all of the available receptor molecules.
- The magnitude of a biological effect is not necessarily directly proportional to the extent of receptor occupation by the substance, but is some monotonically increasing function of the concentration of the complex of receptor with substance, which provides a stimulus leading to the expression of an effect through a complex cascade of events.

Stephenson decomposed the function relating the magnitude of effect to the concentration of complexes of substance bound to receptors, into two functions. One function describes a linear, substance-dependent mechanism; the second function describes a nonlinear, substance-independent mechanism, one that usually involves a cascade of steps with complex interactions, feedback loops, and external physiological regulation.

If a substance causes two effects in an animal, and if an antagonist blocks both effects to the same extent, both effects probably result from binding to the same receptor. If the antagonist blocks these effects differentially, different kinds of receptors probably are involved. If **K** for an agonist is the same for both effects, the receptors are quantitatively identical. These aspects of receptor theory led to quantitative classifications of different kinds of receptors. Dioxin-related substances, the prototypical substances targeted by ATSDR's mixtures approach, usually act by binding to the same cellular receptor, *Ahr* (Byrd, 1995; Byrd *et al.*, 1995a; Byrd *et al.*, 1995b; Byrd *et al.*, 1998).

ATSDR's mixtures approach assumes that a single number can characterize the biological activity of a substance in a mixture, like different dioxin-related substances binding to *Ahr* and generating biological effects characteristic of dioxin, whereas general receptor theory requires two numbers to characterize the properties of a substance in isolation. So, for dioxin-like substances, which bind to a receptor, ATSDR's mixtures approach cannot be right.

(3) ATSDR's mixtures approach uses a weight of the evidence process, based on subjective opinions about the properties of a substance within a mixture. For example, ATSDR proposes the use of factors developed by the World Health Organization, which spaced numerical values at tenfold intervals and which aimed to reflect policy objectives. Inevitably, such a weight of the evidence process will make ATSDR's assessments needlessly subjective. ATSDR has needlessly cloaked this subjectivity with a numerical process.

(4) Contrary to ATSDR's mixtures approach, only a scientific assessment of

the toxicity of a mixture can reveal the properties of a mixture in a nonsubjective way through a direct evaluation of a mixture, measurement of the toxicity of a mixture, or an assay of a mixture. ATSDR's mixtures approach lacks empirical support. The midpoint of an exposure-response relationship does not necessarily imply occupation of half of the available receptors. Thus, the relationship between receptor occupation and extent of effect often is nonlinear, and general receptor theory subsumes classical receptor theory as a special case.

ATSDR's authorizing statute, the Comprehensive Environmental Response, Compensation and Liability Act (CERCLA), requires that ATSDR cooperate with the U.S. National Toxicology Program (NTP) to conduct research about health effects. NTP recently assayed a mixture [TR-526] of three dioxin-like substances (NTP, 2004) for biological effects. The mixture of these three substances is an experimental prototype for ATSDR's mixtures approach, in comparison to a mathematical processing of data from bioassays of the three substances in isolation from each other.

(Technically, CTRAPS objects to NTP's bioassay as a test of ATSDR's mixtures approach. NTP's scientists knew beforehand that two of the substances in the mixture had similar metabolisms and had similar biological activities. The substances chosen for the experiment were not present in typical concentrations. Instead, NTP mixed the substances at equivalent concentrations in corn oil, yet exposed the rats to less than maximum amounts, decreasing the possibility of detecting partial agonist activity.)

However, NTP presented a preliminary analysis of the results of the bioassay of this mixture at the 2005 Society of Toxicology's Annual Meeting in New Orleans (Abstract No. 33, "Testing the toxic equivalency factor hypothesis: The NTP dioxin/PCB cancer bioassays" by N. Walker, M. Wyde, P. Crockett, A. Nyska1, J. Bucher and C. Portier). NTP's evaluation used administered dose as the exposure metric. Overall, NTP found that the data were consistent with additivity of potency-adjusted exposures of substances in mixtures in carcinogen risk assessments. As interpreted by NTP staff, these data do not support ATSDR's contention that mixtures sometimes deviate from expected additivity. Additional experiments that do not test for deficiencies in ATSDR's mixtures approach will not resolve the discrepancy. ATSDR and other Federal agencies continue to conduct experiments which can only be interpreted as supporting their policies. In this instance, the Environmental Protection Agency's desire to use toxic equivalency factors (TEFs) conflicts with ATSDR's desire to designate substances which deviate from additivity in mixtures.

(C) ATSDR's mixtures approach could, but did not, use experts' subjective assessments correctly to decide which mixtures most merit experimental evaluations. ATSDR's mixtures approach should comprehend the difference between

staff opinions about research needs and opinions based on expert opinion. Instead, CTRAPS's consultants regard ATSDR's mixtures approach as representing a failure of risk characterization (EPA, 1995; NRC, 1996; SPS, 2000).

(D) ATSDR needs a stopping point, beyond which experimental evaluation of a mixture will have no value, or some other way to set priorities on research needs. ATSDR does not need to test every possible combination of substances in every possible mixture. The U.S. Congress referred to feasibility in CERCLA. Feasibility can either mean practicality (gathering such data will prove impossible) or cost/benefit (gathering such data will prove too costly). Value of information, a decision analysis technique, will provide ATSDR with some insight into the relative merits of different research needs. In addition, the U.S. Congress asked ATSDR only to evaluate mixtures as found at hazardous waste sites. ATSDR needs to give some practical definition to this idea, perhaps by sampling effluents from waste sites on a weighted basis.

CTRAPS opposes the idea that Federal agencies, including ATSDR, should give equal weight to every uncertainty. In setting out research needs, ATSDR currently compares its perception of the available information to a checklist and lists all of the differences between the two lists as "gaps," or research needs. All of these "gaps" do not equally merit remedy. Many consist of unneeded data. Many of these data gaps lack cost justification. In contrast, some have high priorities. ATSDR could use "policy" and estimated toxicities of substances found at waste sites, as assigned by expert opinion, to decide which mixtures might merit experimental measurement and comply with its legislative requirements.

NTP's scientists generated some general principles about mixtures (Yang and Rauckman, 1987). The list below includes some of their principles, rephrased in application to a feasible mixtures approach.

> **(1) Individually testing all chemical substances found at solid waste sites is not possible.** Where the Federal government has extensively tested a substance as part of its regulatory oversight, ATSDR might defer to the regulatory judgements of other agencies, which are based on data.
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> **(2) Testing all possible mixtures found in the vicinity of waste sites, is not possible.** However, ATSDR can sample mixtures on some weighted basis (population exposure, geography, etc.) and calculate averages (Byrd and Cothern, 2000). ATSDR also can set priorities about which mixtures most merit bioassay for which properties, among the average values. Experimental discovery that certain substances do not inhibit or synergize with other substances in practically defined mixtures, essentially will remove a substance from contention.
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> **(3) Representing all possible exposure pathways of mixtures from solid waste sites is not possible**. Instead, ATSDR needs to define and test some representative mixtures. Pending such definition, NTP's test data about mixtures

of dioxin-like substances are reassuring. These data do not reveal a need for concern about inhibition or synergy between substances found in mixtures in the vicinity of waste sites.

(4) Many of the biological effects of mixtures do not merit experimental definition. CTRAPS is not aware of direct experimental studies of the human chronic exposure to mixtures found at solid waste sites. The most relevant scientific data would come from epidemiology studies of organisms, including humans, in the vicinity of solid waste sites. ATSDR has conducted such studies without finding remarkable effects. These epidemiological observations are reassuring. ATSDR's epidemiology studies do not yield evidence of a previously unanticipated biological effect, and these studies suggest that the additional risk to a population in the vicinity of a waste site, if any, is low.

(E) The nature, direction and magnitude of a biological interaction, if any, between substances in a mixture will remain uncertain until ATSDR develops a new mixtures approach based on experimental evidence. Until such redefinition, CTRAPS recommends that ATSDR publish its own interpretation of the data provided by NTP, including recent bioassays of mixtures of dioxins and earlier, more practical work aimed at actual mixtures. (See the SOT abstract by Walker and coworkers cited above and the 1987 paper by Yang and Rauckman).

DOCUMENT AVAILABILITY: ATSDR's notice [*Federal Register 69(245):* 76768-76769 (December 22, 2004)] contends that the Agency submitted the draft guidance manual for the assessment of joint toxic action of chemical mixtures to both peer-review and public review processes and that changes in the document reflect those reviewers' comments. The documents made available to the public in October of 2004 do not fully explain ATSDR's mixtures approach. The guidance manual for the assessment of joint toxic action of chemical mixtures was not easily obtained, based on the information made available in October of 2004.

ATSDR included an early version of the guidance manual on a CD-ROM disk described as the ATSDR ToxProfiles 2004 (TM) including ToxFAQs and released it in October of 2004. However, this CD-ROM and the guidance manual first became known to CTRAPS until after publication of the *Federal Register* notice in December of 2004. ATSDR's mixtures approach was, at this time, available only in a separate pdf file. In addition, ATSDR announced an international conference on scientific developments and progress in the toxicology of chemical mixtures on September 10-12, 2002, in Atlanta, GA. In addition, ATSDR cosponsored a Society of Toxicology (SOT) Contemporary Concepts in Toxicology meeting titled "Charting the Future: Building the Scientific Foundation for Mixtures, Joint Toxicity and Risk Assessment" on February 16–17, 2005, in Atlanta, GA. Neither of these meetings constituted adequate public notice and comment about ATSDR's mixtures approach.

Thus, CTRAPS only filed a written request for comments on ATSDR's CD-ROM during the comment period for this notice. The CD-ROM does not explain ATSDR's mixtures approach. Instead, CTRAPS electronically obtained an amendment to ATSDR's guidance manual from

ATSDR's web site at http://www.atsdr.cdc.gov. Further, as of March 14, 2005, neither the summary page nor the section of ATSDR's web site, titled "ATSDR Documents Released for Public Comment" contained any mention of ATSDR's "Guidance Manual for the Assessment of Joint Toxic Action of Chemical Mixtures." Instead, it states: "ATSDR seeks your input on documents released for public comment. Please address your comments as indicated in the document on which you are commenting. Copies of ATSDR documents are available from the ATSDR Information Center. Call, toll-free, 1 (888) 422-8737 or e-mail the Information Center. Please note: This listing may not represent all materials released by ATSDR for public comment."

PEER REVIEW: ATSDR's notice [*Federal Register 69(245):* 76768-76769 (December 22, 2004)] contends that the Agency submitted the draft guidance manual for the assessment of joint toxic action of chemical mixtures to both peer-review and public review processes. ATSDR asserts that changes in the document reflect reviewers' comments. CTRAPS does not oppose peer review (NEPI, 1996; NEPI, 1998). However, peer review cannot substitute for public notice and comment.

LEGISLATIVE AUTHORITIES: Section 104(i)(3) and (5) of the Comprehensive Environmental Response, Compensation, and Liability Act of 1980 (CERCLA) requires ATSDR to assess the adequacy of information about health effects for priority hazardous substances and their mixtures with other substances, as found in the environment, not in all theoretically possible permutations. Further, in the absence of information about a mixture that ATSDR might need to assess a waste site, CERCLA requires that ATSDR, in cooperation with NTP, initiate research to determine the health effects of the mixture. CTRAPS see no reason why ATSDR should hold these requirements in abeyance. However, these requirements are contrary to ATSDR's mixtures approach. CERCLA also directs ATSDR to develop methods, where feasible, to determine the health effects of combinations of substances, as commonly found. The Guidance Manual fails to provide methods for ATSDR staff to determine the health effects of commonly found mixtures, proceeding from bioassay data about the mixture.

The Food Quality Protection Act (FQPA) of 1996 does require a consultation between the U.S. Environmental Protection Agency (EPA) and the Department of Health and Human Services (DHHS). However, ATSDR has an improbable stretch to reach a mandate for its mixtures policy based on this clause (Byrd, 1998). DHHS could consult with EPA without finalization of any interaction profiles or the overarching policy hidden in the Guidance Manual. DHHS has not formally delegated the consultation to ATSDR. The factors listed in FQPA for EPA to consider do not restrict the factors that ATSDR might want to take into account in its mixtures approach. FQPA does not cite ATSDR. Thus, CTRAPS does not understand how ATSDR asserts a mandate to develop a mixtures program based on FQPA.

DISCLAIMER: The two scientists commenting on ATSDR's guidance manual for CTRAPS have publically commented about the related subjects of dioxin-containing mixtures and risk communication. Both scientists have published documents and given talks about these subjects.

Signed,

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