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Peer Review of EPA's Motor Vehicle-Related Air Toxics Study

Submitted to:

United States Environmental Protection Agency
Office of Mobile Sources
National Vehicle and Fuel Emissions Laboratory
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The review will take the form given in the Statement of Work. General comments will be incorporated at appropri points within the five major points for review. (The following abbreviations are used throughout the review: p.-page; §-sec ¶-paragraph.)

1. *Assessment of modeling of hypothetical day in the summer of 1990 in St. Louis using UAM-Tox, a version of UAM that explicitly models toxics. Comment on the validity of assumptions used in the model, and results for benzene, formaldehyde, 1,3-butadiene, acetaldehyde, and POM.*

This review does not include a comprehensive discussion of the UAM, and would probably be outside the scope of this document. The overall assumptions of the UAM are contained in ¶2 of §5.4.5 and certainly are accep as such in terms of grid sizes, mixing heights, etc. The incorporation of benzene and 1,3-butadiene are the most straightforward species to incorporate as separate species in the UAM (i.e., UAM-Tox). Of the two species, benze is possibly handled somewhat more easily that 1,3-butadiene, since benzene reacts substantially only with OH (duri the day), while 1,3-butadiene has substantial removal rates by OH and ozone during the day and ozone and NO_3 at night. Accurate predictions of ambient concentrations of these chemicals is undoubtedly more dependent on accu emission rates rather than loss rates by processes such as chemical reaction. On the other hand, formaldehyde an acetaldehyde are formed in both primary and secondary processes and predictions of these concentrations are high dependent on the accuracy of chemical module of the UAM.

In the overall description of the UAM, there should be some discussion as to how the UAM and UAM-Tox handles mixing between cells and the assumptions involved in mathematically performing the mixing function.

(The last sentence in ¶5 of §5.4.5 is unclear and should be rewritten. The authors appear to be stating tha Houston is expected to show little benefit with the use of reformulated fuels, since the HC/NO_X ratio in that airshed extremely high (due to refinery contributions) and changing the hydrocarbon composition of an already hydrocarbo rich area is expected to have negligible effect. On the other hand, Baltimore-Washington, DC having a much lower HC/NO_X ratio with a much higher hydrocarbon contribution from mobile sources is expected to show a much grea effect from the use of reformulated fuels.)

The major assumptions in selecting the hypothetical day in the summer of 1990 based on a historical episo of 13 July 1976 is outlined in ¶6 of §5.4.5 (p. 5-19). Clearly SAI and the authors have considerable experience wit this episode, especially the meteorological aspects, and its selection is wise. The authors are also correct in noting pollutant levels in 1976 were no doubt substantially higher than they would have been in 1990. The major assumptions that arise which should be addressed are: (1) has increased urban growth or other changes over the 1 period between 1976 and 1990 influenced meteorological factors substantially since the original study was carried (2) are emission sources of hydrocarbons substantially different 14 years later and what validation data is available emission sources of the toxic compounds? (3) are any experimental data on the concentrations of the compounds interest from either 1976 or 1990 available for comparison with the model? This last issue is the most important. What ambient benzene data is available for St. Louis? (Is the data in Appendix C the extent of the ambient data?) Were any of the available experimental measurements taken under conditions that could be used to compare the mo Clearly, some discussion of the uncertainties involved in the results from use of the UAM-Tox are essential. In particular, some discussion of the largest sources of uncertainty in predicting the atmospheric concentrations shou provided. A map of St. Louis with the location and size of grid cells (8,11) and (8,13) and the prevailing winds sh be provided for clarity. Some additional comments are provided on a compound-specific basis.

Benzene. An examination of Appendix B show average benzene levels for St. Louis ranging from 3 - 10 ppb over the period 1987-1989. Based on these data, it is reasonable to assume that average 1990 benzene levels i Louis would be in the range 2 - 5 ppb based on these data. However, the UAM-Tox modeling in Appendix D shov benzene values ranging between 0.1 and 0.8 ppb for the hypothetical day in 1990 with an average value of approximately 0.5 ppb. This large discrepancy suggests a substantial systematic error is present either in the mode in the measurements. (Let me suggest one possible source of the discrepancy. Some check should be performed ensure that the units for the ambient concentrations and the modeling results are the same, that is ppbv or ppbC. N that ambient measurements are generally reported as ppbC, whereas most modeling results are frequently calculate a molar or volume basis, that is, ppbv. In this case, 1 ppbv of benzene is equivalent to 6 ppbC.) If the units as presented are, in fact, on the same basis, some explanation as to the difference between the ambient concentrations modeling results should be discussed, in particular, the motivation for the selection of UAM Cell (8, 11) for presentation and the degree to which that cell is representative of typical St. Louis concentrations.

Formaldehyde. It is not clear the basis for the statement in §6.4.4, ¶5 (p. 6-13), "The comparison of simulated concentrations with ambient measured concentrations showed good agreement for formaldehyde." Amb data for St. Louis from Appendix C, simply give averages which appear to be substantially lower than the average value from the hypothetical data. The statement should be qualified to reflect that the small number of ambient poi under a variety of conditions can only provide very limited validation of the model. (My guess is that any model th yielded formaldehyde concentrations between 1 and 10 ppbv would be considered to show good agreement with a the formaldehyde data in Appendix C.)

As noted §6.4.4, ¶6 (p. 6-13), the photolysis data from Moortgat *et al*. is the appropriate data to use in the model for formaldehyde photolysis. However, it should be recognized that for appropriate actinic wavelengths approximately one-third of the photolysis reaction goes to form radical products; two-thirds of the reaction goes to form non-radical products under most conditions.

As a final note, shouldn't formaldehyde concentrations be compared in grid cells (8,11) and (8,13) as were acetaldehyde concentrations later in Section 8?

1,3-Butadiene. It is not clear how the stationary and mobile inputs to 1,3-butadiene in Figure D-3 can be decreasing after 10:00 h, and yet the inert portion of 1,3-butadiene can continue to increase. (I had thought that inert component was the sum of the two components in the absence of chemical reaction rather than an integrated value.) Does the inert term contain non-chemical losses? Perhaps the explanation of the inert component could be somewhat improved.

It looks as though the model was terminated a little early in the simulation for 1,3-butadiene. In §7.4.4; ¶4 the text states that comparison of the simulated concentrations with ambient concentrations showed good agreeme What constitutes good agreement and what is the reference (literature or report) for the 1990 ambient data for St. Again in the discussion of the Baltimore-Washington and Houston area simulations for 1,3-butadiene, I would ask t authors to clarify whether concentrations are in ppbC or ppbv.

Acetaldehyde. For the most part, comments for acetaldehyde parallel those for formaldehyde. The third paragraph in §8.4.4 (i.e., "Secondary ALD2 is produced....") should be eliminated. The fourth paragraph should be rewritten for clarity. The fifth paragraph contains information on the grid cells that should be introduced in Sectio particularly the motivation for selecting grid cell (8,11) for examination. The average residence time of an air mass cell (8,11) would provide useful information in the sixth paragraph of §8.4.4.

What is the origin (or reference) for ambient measurements of acetaldehyde? If formaldehyde and acetaldehyde data were available, measurements for the higher aldehydes are probably also available since the ambi measurements were undoubtedly obtained using DNPH cartridges or impingers. This would give some experiment guidance as to the likelihood that urban concentrations of higher aldehydes were comparable to formaldehyde and acetaldehyde, as stated in §8.4.4; ¶8 (p. 8-12).

¶6 §5.4.5.1: It would appear to me that the residence time calculations fall out of the UAM from the chemistry of a single cell. Thus, agreement between the two methods does not result from truly independent determinations.

It would be valuable to have a table which contains the major input and output parameters for the model employed. This could be done in a fashion similar to the residence time tables and would include most of the value discussed in §5.4.4.3. If the purpose of the residence time calculation is to provide input for exposure assessment absolute numbers are indeed important, since people are exposed to absolute concentrations of toxics and not relati concentrations.

POM. Some discussion would be valuable to clarify loss of POM from deposition of particulate matter from the atmosphere as opposed to loss of POM itself on the particle through sublimation or reaction while the particle remains aloft in the troposphere.

2. *Review of the EPA's discussion of atmospheric reactivity and residence time for benzene, formaldehyde, 1,3-butadiene, acetaldehyde, and POM.*

I will give some general comments initially. This will cover the aspects of atmospheric reactivity and residence times for all compounds discussed. Somewhere in the beginning of the discussion of lifetimes, it should explicitly noted that rate constants and concentrations refer to conditions in the mixing layer of the troposphere and would not necessarily hold throughout the troposphere. I find the term *lower atmosphere* (p. 5-12) to be very vague and suggest that alternate term be utilized, if feasible. *Lower troposphere* is much better, but generally includes an altitude much higher (ca. 4 km) than the mixing layer.

The discussion of the atmospheric transformation of the toxic compounds under consideration appears to fairly well grounded on a theoretical basis. It is important for the authors to note that rate needs to be distinguished from rate constant; the term rate includes both the rate constant and concentration. This distinction should be noted the second and third paragraphs of p. 5-12.

The authors appear to have a resistance to including technical data such as rate constants and OH concentrations choosing instead to give qualitative descriptions of these terms. In some cases, inclusion of the quantitative data would be valuable, especially in evaluating the origin of certain estimates.

Regarding the discussion of ambient concentrations in the second paragraph of p. 5-13, it is important to r that atmospheric lifetime (or residence time) is but one component that must be included to determine the ambient concentrations. It is also important to note that at the present time, ambient concentrations of toxic compounds ca be accurately *predicted* based solely on emission rates, atmospheric dispersion, chemical removal and formation, e At the present time, experimental measurements of toxic compounds are the most reliable means of obtaining ambi concentrations and they certainly must be used to validate air quality models for toxic compounds.

In the last sentence on p. 5-14, the context of the passage suggests that the sentence ought to read, "shoul considered" rather than "should not be considered."

The authors should provide a short discussion on how changes in the mixing height affect concentrations the mixing layer during the course of the day and night. Changes in the mixing height is an important determinant i dilution during the course of a day especially where conditions for an inversion are present. Moreover, lower mixi layers at night can profoundly affect ground level concentrations at night particularly for compounds having high deposition velocities.

Benzene. Of the processes discussed in §5.4.2.1, only reaction by OH is of significance in terms of atmospheric loss of benzene and even reaction with OH is relatively slow ($k_{OH + benzene} = 1.4 \times 10^{-12}$ cm^3 $molec^{-1}$ s^{-1}) compared to the OH reaction rate with other volatile organic compounds. As noted, reactions with $O(^3P)$, O_3, NO_3 and Cl with benzene are of minor consequence in the lower troposphere. Relatively few studies have been conduc of the reaction products from benzene. Those products which have been detected include those mentioned in Sect 5.4.2.2. It should be noted that most studies have identified approximately 50% of the carbon products from the reaction of OH with benzene.

The discussion of atmospheric residence times in Section 5.4 lead to what appear to be very low residenc times in Los Angeles, St. Louis, and Atlanta under clear-sky day conditions. While it is recognized that the use of model for calculation of lifetimes can allow inclusion of minor processes such as dry deposition, it must be acknowledged that loss of benzene occurs almost exclusively by reaction with OH. If one back calculates OH concentrations required to give 30 h lifetimes in St. Louis or Atlanta one obtains a daytime, clear sky OH concentra of 7×10^6 molec/cm^3, a value that seems unduly high. Justification for these OH concentrations should be given o least it should be checked to ensure that no systematic errors are present in the determination. It appears that the model generates these high OH values because the simulations were conducted for severe ozone concentrations. However under these conditions it would expect the OH concentration to be the most uncertain due to the substant

loss and regeneration where very high precursor levels are present. How do the OH values produced by the model compare with those that have been observed in the few experimental studies that have been conducted? In any cas references justifying these OH levels should be provided, if they exist.

Are dry deposition velocities for benzene available or were they estimated?

With respect to the reaction products, it is important to note that the glyoxal yields are on a molar basis an thus the 24% molar yield represents an 12% carbon yield for the reaction of OH with benzene. Thus, the known (measured) yield of reaction products from the reaction of OH with benzene is 39%. Thus, three-fifths of the react products are of unknown identity and yield.

Formaldehyde (HCHO). The same considerations for the benzene residence time also hold for the HCHO residence time. As noted in the text, the daytime residence time is only a few hours. As in my comments c benzene, it seems that the OH concentrations from the model is high. It has always been my understanding from calculations, that during the day under clear sky conditions photolysis could dominate the loss of HCHO by approximately a factor of 2. Again OH concentrations should be verified. All other aspects of the discussion appe to be accurate.

If the HO_2 + HCHO reaction is utilized for the night time residence time, some justification of the HO_2 concentrations generated by the model should be made. (At the very least the HO_2 concentrations generated by the model should be made available.)

1,3-Butadiene. Again, for the data for 1,3-butadiene, it is important to distinguish whether the units in plots are ppbv or ppbC. As with benzene, any available ambient measurements in St. Louis in 1990 should be compared to the model. The text in §7.4.3; ¶3 discusses the short night time residence time for 1,3-butadiene presumably due to reaction with NO_3 radicals, and yet the data in Figure D-3 shows a rapid rise in 1,3-butadiene concentrations after 20:00 hours LST. This is surprising since NO_3 concentrations would be expected to be at the greatest relative concentration at sunset, not withstanding evening emissions.

I also find the statement (§7.4.3; ¶6) that "although the daytime residence times are accurate to about a fa of two, nighttime residence times are certain only to within an order of magnitude" somewhat incredulous. Assum the accuracy of the rate constant for OH + 1,3-butadiene is accurate to 25% and the NO_3 + 1,3-butadiene is accura a factor of two, the major portion of the uncertainty of the respective residence times lies in the estimation of the C concentration vs. the NO_3 concentration. I would expect the NO_3 concentration to be no worse predicted than the concentrations. NO_3 concentrations are formed from NO_2 + O_3 both relatively stable molecules for which measurement techniques are available. OH on the other hand is largely dependent on the HO_2 concentrations whicl at best difficult to measure in the atmosphere. Both OH and NO_3 are in dynamic equilibrium between formation an removal. It is difficult to understand how OH concentrations could more accurately be predicted by the model tha NO_3 concentrations.

Acetaldehyde. The value of the OH rate constant for acetaldehyde is at least 50% higher than that for formaldehyde. The photolysis of both formaldehyde and acetaldehyde can lead to radical products. The implicatio §8.4.1; ¶1 that formaldehyde does not form radical products is incorrect. For formaldehyde, one-third of the photolysis reaction leads to radical products (ultimately, 2 HO_2 molecules) and two-thirds leads to non-radical products. (For acetaldehyde, as noted in the text, the photolysis reaction leads exclusively to radical products at actinic wavelengths.)

Background material, such as that given in §8.4.1.1, should be handled earlier in the text. (For example, tl is no need to handle nomenclature issues at this point in the text.) For acetaldehyde to be formed, the precursor m have a methyl group.

In §8.4.1.3, it should be noted that the reaction of peroxyacetyl radicals with NO_2 is a chain terminating process while the reaction of peroxyacetyl radicals with NO is chain propagating. Also in the paragraph, the photolysis of acetaldehyde produces CH_3 radicals which then add O_2 to form CH_3O_2.

POM. The discussion of the atmospheric lifetimes and residence times for POM species is accurately depicted in the discussion. This is a very difficult problem to address as noted in the text. Most issues are handlec about as well as they can expect to be.

3. *Discussion of approaches the EPA could use to better incorporate information on atmospheric reactivity and residence times into risk assessment. Comment on the role of atmospheric transformation in affecting the mutagenicity and carcinogenicity of motor vehicle emissions, and on the importance of atmospheric transformation products in assessing risk from motor vehicle emissions (e.g., peroxyacetyl nitrate, acrolein, and secondary formaldehyde). Discuss the likely effect of such approaches on conclusions and estimates in the study.*

The approach that EPA used to consider atmospheric reactivity and residence time overall was an excellen approach. However, as noted above I question some of the radical concentrations (particularly OH concentrations generated by the model used to determine the atmospheric lifetimes. However, as a means of providing a comprehensive evaluation of the feasible loss mechanisms, the model provides an excellent means of doing this. T without a detailed examination of the workings of the model, I can present no better method for EPA to incorporat information of atmospheric reactivity to provide information on residence times.

The rest of the discussion will focus on the role of atmospheric transformation in affecting mutagenicity a carcinogenicity of motor vehicle emissions. Over the last ten years, experiments have been conducted by a fair nu of investigators to examine the extent to which the chemical constituents found in automotive exhaust could lead tc formation of genotoxic products. For example, Kleindienst, Shepson, and co-workers conducted experiments to determine the extent to which hydrocarbons emitted into the atmosphere could undergo transformations by normal oxidative processes to produce species which were significantly more genotoxic than the starting materials. These experiments involved smog chamber irradiations of both simple and complex mixtures. Of the compounds under consideration for this study, only acetaldehyde[1] was tested for formation of genotoxic products. Substantial mutag activity was observed for the products of the oxidation with the bacteria *Salmonella typhimurium*, strain TA100. For this photochemical system, most of the products of the oxidation are known and it was found that the majority the mutagenic activity was due to a single product, peroxyacetyl nitrate.

Measurements of the mutagenic activity of the products from the photooxidation of toluene have been alsc measured. While toluene is not considered to be a motor vehicle-related air toxic, it is found in substantial concentration in automotive exhaust. The mutagenic activity of the products from this system have been measure number of studies using Salmonella[2,3] as well as other assays.[4] Comparisons of the production of mutagenic produ from aromatic precursors with that of other type of hydrocarbons, have suggested that aromatic compounds lead t majority of the activity found in the irradiated products from automotive exhaust.[5]

The difficulty in these types of studies is determining the specific chemicals which give rise to the observe mutagenic activity. In recent work of Kleindienst *et al.*,[6] it was found that in olefinic and aromatic systems, most mutagenic products arise from secondary products formed during the irradiation, as opposed to primary products. This suggests that most mutagenic products are formed from reactions of carbonyl compounds formed in the syst However, results from earlier work[7] suggests that the formation of mutagenic products is highly dependent on the presence of NO_X in the system. That is, NO_X limited systems tend to be less mutagenic. That is the formation of mutagenic products increases more rapidly than the simple increased conversion of reactants to products. These c suggest that limiting the NO_X input into urban atmospheres would limit the formation of mutagenic products, althou additional research would be required to confirm this observation. The observations would further bolster the argu for NO_X controls in addition to hydrocarbon controls.

Measurements have also been conducted by Löfroth and co-workers to measure the mutagenic activity of products from the photooxidation of 1,3-butadiene[8]. A major product from the photooxidation of this compound, i acrolein which also is considered to be an air toxic. In the study of Löfroth, products from 1,3-butadiene were sh

to be approximately 5 times more mutagenic in *Salmonella typhimurium*, Strain TA100 than similar oxidations with propylene. However, this study can only be considered a survey study, because no attempt was made to understand the product distribution from this reaction and to consider the extent of reaction for which the measurements were made. This is potentially an important consideration, in that Kleindienst and co-workers[6] have found substantially higher mutagenic activity for products formed in the toluene/NO_X and propylene/NO_X systems greater extents of reaction.

In summary, the oxidation of hydrocarbons does lead to products that are substantially more mutagenic th the precursor. However, the significance of these observations with respect to *human* health impacts are currently unknown. Recent measurements of the Heddle *et al.*[9] to examine *in vivo* mutagenesis of PAN were inconclusive. Clearly additional research needs to be conducted in this field. Finally, Kleindienst *et al.*,[5] have provided some information on the effect of atmospheric transformations on the mutagenic activity of POM on particulate matter. general the mutagenicity decreases on a potency basis, but increases somewhat on a volume basis. (An expanded discussion or additional references for these issues can be provided, if desired.)

4. *Discuss how results from the EPA's Integrated Air Cancer Project should be applied to analyses of health risks from motor vehicle-related air toxics.*

The report overall did an excellent job of presenting the results found from EPA's Integrated Air Cancer Project (IACP). With respect to particulate matter from automotive emissions, it found that in Boise, Idaho approximately three-quarters of the particulate matter was due to emissions from wood burning with a much small fraction due to automotive emissions, that is, ug/m^3. However, the potency of particulate matter from automotive emissions was approximately a factor of three higher than particulate matter from wood burning emissions.

In its original experimental design, the IACP sought only to comprehensively examine the health risk from POM. In this case, cancer risk could only be attributed to compounds found on the particulate phase and generally were considered to result from automotive and wood burning emissions directly. A demonstration of an excellent approach for applying the experimental data of the Integrated Air Cancer Project to determination of health risks fr automotive emissions is best demonstrated by Lewtas *et al.*[10] This study which has already been considered in this report considers composite effects from POM from wood burning and automotive exhaust . In their investigation, examined health risk by combining source apportionment and exposure assessment with tumorigenicity studies for extracts from particulate matter. Thus, an examination of the health risk did not include risk associated with the exposure to benzene, 1,3-butadiene, formaldehyde, or acetaldehyde. Moreover, no consideration was given to pro formed in the gas phase from precursors which originated from motor vehicle emissions (exhaust and evaporative emissions). Of course, the major reason for focussing on the POM constituents in the particulate phase is previou work showing mutagenicity and carcinogenicity of these compounds. However, it is also possible that with expos logs from the Boise study and indoor and outdoor concentrations available for benzene and the other motor vehicle related air toxics that some estimate of the risk from these compounds might also be feasible.

Finally it is important to recognize that the IACP scrutinized only one substantive aspect of the health risk problem, that is, carcinogenesis and other related end points that represent chronic risk. (And for this aspect compounds in the particulate phase were examined in particular depth.) Thus, while the IACP serves as a starting point for these types of studies, it by no means represents a comprehensive picture of the health risk from exposur automotive emissions.

5. *Inform the EPA of additional studies, analyses or other information on atmospheric reactivity and residence times that were not included in the EPA study. Discuss the likely effect of this information on conclusions and estimates in the study.*

The study was extremely comprehensive for the major compounds under consideration. Relatively little information on these compounds was excluded from this study. However, I have included a few references whic

provide additional information form some of the topics considered in the report on the final page of the review.

References

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2. Shepson, P.B., T.E. Kleindienst, E.O. Edney, G.R. Namie, J.H. Pittman, L.T. Cupitt, and L.D. Claxton. 1985. The mutagenic activity of irradiated toluene/NO_X/H_2O/air mixtures. *Environ. Sci. Technol.*, **19**, 249-255.

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9. Heddle, J.A., P.B. Shepson, J.D. Gingerich, and K.W. So. 1993. Mutagenicity of peroxyacetyl nitrate (PAN) *in vivo*: Tests for somatic mutations and chromosomal aberrations. *Environ. Molec. Mutag.*, **21**, 58-65.

10. Lewtas, J., R.B. Zweidinger, and L. Cupitt. 1991. Mutagenicity, tumorigenicity, and estimation of cancer risk from ambient aerosol and source emissions from woodsmoke and motor vehicles. *Proceed. 1991 Air and Waste Managem. Assoc. Ann. Meeting*, Paper 91-131.6.

Additional References

Faust, B.C. Aqueous-phase photochemical reactions in oxidant formation, pollutant transformations, and atmospheric geochemical cycles. *Environ. Sci. Technol.* **28**:217A-222A. Reference presents atmospheric losses in the aqueous phase and effects of cloud cover and transformations in the condensed phase. This is one aspect that the report did not cover in substantial detail. It could be important for formaldehyde, particularly under the assumption that rainout leads to subsequer entrainment into the atmosphere following evaporation.

Victorin, K. and M. Stahlberg. 1988. Photochemical formation of mutagenic compounds from alkene and ozone or nitroger dioxide. *Environ. Molec. Mutagen.* **11**, 79-90. References of these authors include some additional work on the formation of mutagenic species in the gas phase.

Review of "EPA Motor Vehicle-Related Air Toxics Study"
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Specific Comments

5.6 **Carcinogenicity Of Benzene and Unit Risk Estimates**

Pg. 5-35, Human Data - In 1991, a meeting was held on "Health Effects of Gasoline" now published in Volume 101, Supplement 6 of "Environmental Health Perspectives". That meeting was attended by a number of representatives from EPA, including those from the Ann Arbor office that prepared this document. There are three recent human studies relating benzene exposure and leukemia in worker populations that should certainly be included in the discussion, and attempts be made to use the data in the risk calculations rather than rely solely on the Rinsky study.

Pg. 5-37, 5.6.1.3 Data Sets Used For Unit Risk Estimate

See comments above. The Rushton and Schnatter studies appear to be of value in the unit risk calculation, and the use of three separate studies done in different populations would give some sense of the variability in the response and give a truer estimate of the range of uncertainty. Another interesting exercise would be to take the best sets of animal data and calculate the unit cancer risks from these studies and compare them to the data derived from human sources. The results of such a comparison would seem to be important for better understanding the methods by which risk assessments are calculated, since there are both human and animal data. While the potency factors are described in the section 5.6.2 Other Views and Risk Estimates, it would be very interesting to draw together all the risk assessments derived from human and animal studies in a single table.

Pg. 5-41, l. 23-30 - While EPA did not do the risk assessment calculation noted in these lines, possibly some comment is in order relating to the use of the preputial gland as the target organ for the calculation. This seems scientifically inappropriate and, to be sure, somewhat bizarre. Indeed, some comment might be useful to indicate that the induction of leukemia and lymphomas in animal studies, even a very high doses, is not a frequent finding, raising serious questions about the applicability of animal studies to humans specifically in connection with benzene.

Pg. 5-44 & 5-45 - This apologia by the Agency is not needed here and detracts from the presentation. It borders on whining. Indeed, most of the commentary states that Chan does not agree with Clement. This is a matter of opinion, and I found no data introduced that would support the contentions made by the Agency. Given the fact that the Clement report was authored by Krump, who is the originator of the risk assessment methodology at the Agency, and who has probably more experience and credibility in this field than almost anyone, one would naturally tend to believe him rather than someone else. In particular, paragraph 5) on page 5-45 is startling. It is not at all clear how the Agency could state that

they support a theoretical linear low dose extrapolation when there are, in fact, non-linear real data in humans. This sort of response does not do the stature of science at the Agency any good at all.

Page 5-47, 6.5.3.2 Pharmacokinetics - The initial statement in this section may be true, but it is wishful thinking in the absence of data. It could be left out without harming the presentation.

Page 5-33 to 5-36 and page 5-49 to 5-54 - There is a duplication of the information in these two sections relating to animal and human studies on benzene. It would seem that the earlier part could be eliminated in favor of the more complete discussion in the later segment.

6.6 Carcinogenicity Of Formaldehyde and Unit Risk Estimates

Page 6-30, 6.6.1.4 l. 3-5 - The section states that the data were inconsistent concerning the linear or nonlinear relationship between formaldehyde exposure and carcinogenicity. However, in the next section (6.6.1.5, l. 8-10), the Agency states that "Other uncertainties are the marked nonlinearity of the response ...". Clearly the Agency recognizes that the animal experiments reported by Kern et al. display a marked nonlinear response, thus the statement in section 6.6.1.4 is in error and should be made consistent with the later correct evaluation about the nonlinearity of the response.

Pg. 6-30, 6.6.1.5 l. 1 - It is not clear why the Agency selected the 1987 number rather than the 1991 number that was based on the monkey and rat DPX data. This later assessment has been generally accepted on scientific grounds and is certainly more defensible than the earlier number. A recent paper by Conolly and Anderson (Envir. Health Persp. 101 (suppl 6):169-176, 1993) is worth a review by Agency staff. This paper is a well thought-out and complete presentation of the issues surrounding a cancer risk assessment for formaldehyde. The authors explore in detail the several scenarios that have been advanced, including the Agency position, and compare them based on the animal tumor data and experimental studies on DNA-protein cross links. They present a way to address the risk assessment process, presenting several alternatives for understanding the available data. It would make instructive reading for anyone attempting to calculate a risk assessment for cancer from exposure to formaldehyde. With respect to the 1991 number that you indicate is a draft number not to be used formally by the Agency, it would be very useful to indicate to the reader that an alternative method has been proposed by the Agency for the calculation of the risk assessment for formaldehyde and is now under consideration, and if this method were used, what the risk number would be.

Page 6-25 to 6-28 and page 6-42 to 6-48 - As noted above in the comments on the benzene section, the animal and human cancer data are described twice. Some decision should be made on all the sections to reduce the redundancy of presentation of these data.

Page 6-49 - It is noteworthy that the Agency has made use of the auto/oil emissions data, since, this is best contemporary source of emission data, and it is appropriate that these data should be incorporated. In addition, one assumes that the total number of cancer cases is based on the risk assessment number given in Section 6.6.1.5. If the better number from 1991 is used, the number of total cancer cases would fall by an order of magnitude.

7.6 Carcinogenicity of 1,3-Butadiene and Unit Risk Estimates

Page 7-21, 7.6.1.1 and pages 7-37 to 7-41 - The rationale for presenting animal and human carcinogenicity data in two separate places in each report should be given in an introduction to the document. It is quite confusing to have these data separated. It would benefit the document significantly to have all the data of one type in one place.

Page 7-26, 7.6.1.3 - It is not clear why the newer and more rigorous data from the newer NTP carcinogenicity are not used to calculate the unit risk estimates. Certainly this study with its lower doses and longer exposure interval gives a much sounder basis for such calculations. It should also be made clear that the tumor incidence on which the risk calculations are made are based on total tumor incidence, since this issue comes up later in the discussion. It is unfortunate that the Agency is so constrained in the way that it presents risk assessments and that old data and information can only be used. If this is the case, it seems to me that the Agency needs to be frank and honest with the readers of the air toxics study and state clearly that there is a considerable body of new information and that the Agency is working on a revised risk assessment based on the new data. One could even go so far as to propose a provisional risk assessment calculation based on the newest data, both animal experimental and exposure, indicating that the assessment is provisional and that the Agency is forced by statute to use the older number until a new one is formally presented. This would seem to be the most accurate and constructive way to present the case on butadiene.

Page 7.6.3.2 - It is surprising that the extensive pharmacokinetic information demonstrating a clear difference among species in metabolic capability strongly indicating that mice are exceptionally sensitive to butadiene as a carcinogen as compared to humans is not incorporated in the risk assessment calculations. Given the enormous importance that the comparative pharmacokinetics has in the risk assessment process for butadiene, I found that the two pages given to the discussion were inadequate. The authors of the pharmacokinetics section would find it useful to read a very fine review on this subject by Dr. Birnbaum (Envir. Health Persp. Suppl., 101 (Suppl. 6):161-167, 1993).

8.6 Carcinogenicity of Acetaldehyde and Unit Risk Estimates

Page 8-19, 8.6.1 and page 8-26 8.6.3 - Perhaps it would be best to move the "Recent and Ongoing Research" sections immediately after the "Most Recent EPA Assessment" section. This would give a natural flow of historical data and not interrupt the flow of information about the experimental and

human results.

Page 8-28, 8.7 - The estimation of human acetaldehyde exposure is a very uncertain process. The ambient air concentrations will vary widely depending on the industrial processes in an area and the presence of plant biota which can be a significant source of acetaldehyde. In fact, the major source of acetaldehyde exposure relates to the consumption of alcohol by humans. With the very few cancer deaths attributable to acetaldehyde, even under the very conservative approach used by the Agency, it seems of hardly any value to even include this chemical in a risk assessment. If it is included, a much better job will need to be done on explaining the uncertainties in the exposure estimates.

Page 8-34, 8.8.3 - The summary that male reproductive toxicity may be a concern for acetaldehyde is simply not supported by the data. According to Agency estimates of air concentrations of about 0.3 :g/m^3 would yield human doses of about 0.01 :g/kg/day. Compared to the doses used in the experimental studies of 50 to 100 mg/kg/day, the human dose is inconsequential. As noted above, the greatest risk would almost certainly be among those who consumed alcoholic beverages. Any risk from air sources would be minuscule.

9.6 Carcinogenicity of Diesel Particulate Matter and Unit Risk Estimates

Page 9-20, 9.6.1 - See comments above about separation of older and newer data on animal and human evaluations.

Page 9-24, l. 18-25 - The gaseous phase has been shown to contain polycyclic aromatic hydrocarbons and nitrated polycyclics by Dennis Scheutzle, among others. It is surprising that the extensive work done by Scheutzle and his colleagues is not mentioned at all in the review, when it is perhaps the best chemical data of its kind on diesel exhaust. Certainly, it would be inappropriate to disregard the gaseous phase, since it does contain material that are genotoxins and potential carcinogens.

Several citations on gaseous hydrocarbons from diesel exhaust that have mutagenic activity are listed below.

Scheutzle, D., Sampling of vehicle emissions for chemical analysis and biological testing. Health Persp. J., 47:65-80 (1983)

Hampton, C.V., Plerson, W.R., Scheutzle, D. and Harvey, T.M., Hydrocarbon gases emitted from vehicles on the road. II. GC/MS quantitation, emission rates from diesel and spark engine vehicles. Environ. Sci. Technol., 17:699-708 (1983)

If you require additional information, Dennis Schutzle of the Analytical Sciences Department of the Ford Motor Company would be glad to provide you with it.

While I did not review the emission section in any detail, it was clear that nitroarenes have been completely ignored. Some discussion of them is required with respect to their concentration in the air, the potential contribution from diesel exhaust and the difficulties in their measurement because artifacts arising from the formation of nitroarenes in the collection process. Nitroarenes have been reported on numerous occasions on particles from diesel exhaust.

Handa, T., Yamanuchi, T., Ohnishi, M., Hisematsu, Y. and Ishii, T., Detection and average content

levels of carcinogenic and mutagenic compounds from the particulates on diesel and gasoline engine mufflers. Envir. Intern., 9:335-341 (1983)

Hartong, A., Kraft, J., Schulze, Kiess and Lies, K,-H, Identification of nitrated polycyclic aromatic hydrocarbons in diesel particulate extracts and their potential formation as artifacts during particulate collection. Chromatographia 19:269-273 (1984)

Pederson, T.J. and Siak, J.S., The role of nitroroaromatic compounds in the direct mutagenicity of diesel particle extracts, J. Appl. Toxicol., 1:54-60 (1981)

Scheutzle, D. and Perez, J.M., Factors influencing the emissions of nitrated-polycyclic aromatic hydrocarbons from diesel engines. J. Air Pollut. Cont. Assoc., 33:751-755 (1983)

Schuetzle, D., Riley, T.L., Prater, T.J., Harvey, T.M. and Hunt, D.F., Analysis of nitrated polycyclic aromatic hydrocarbons in diesel particulate. Anal. Chem., 54:265-271 (1982)

Möller, L., Torndal, U.-B. and Eriksson, L.C., Risk assessment of nitrated polycyclic aromatic hydrocarbons. Risk Analysis 13:291-299 (1993).

Page 9-30, 9.6.1.3 - With new data sets of Heinrich and Mauderly now available, it would be appropriate to use this information rather than the earlier studies, since the exposure and tumor response data are far more reliable and would yield a more refined risk estimate.

Page 9-30, 9.6.1.4 - The use of a linearized model for the calculation of risk from particle exposure is simply wrong scientifically. It stretches credulity to have a linear model used when the animal carcinogenicity data relating tumor incidence to particle exposure, whether measured as chamber concentration or lung burden, are singularly nonlinear. Both the older and newer studies of Heinrich and Mauderly show this nonlinearity, with tumor incidence rising sharply with an increase in dose. How a linear model could be used in the face on

nonlinear experimental data in inexplicable. While recognizing that the default position of the Agency is to use the linear model, the application of only a modest element of scientific common sense would demonstrate that the use of the linear model is wrong.

The second factor that argues against the use of the linear model is the behavior of the lung when exposed to particles. As the work of Oberdörster has shown, particle responses in the lung are markedly nonlinear, and at the concentration usually experienced in the environment (1-5 : g/m^3), there is no measurable consequence in the lung of such exposure. While the model does attempt to take into account the information available relating particle loading in the lung, it does not address the reality of the nonlinear pulmonary response to particles, with presence of a real and measurable threshold.

Thus, the application of a linear model for calculating cancer risk based on particle exposure is unwarranted and scientifically incorrect.

Page 9-33, l. 12-13 - Though the concentrations of PAH's on diesel particles may be relatively low, they are potent carcinogens are there. If the Agency really believes its linear model for cancel risk modelling, then the ignoring of the PAH in this risk assessment would seem to be in opposition to that policy. Indeed, on the last lines of page 9-39, the draft states " Therefore, the organic components on diesel particles may be importantly involved in the development of lung tumors". It is clear that the PAH from diesel form DNA adducts in the lung that are identifiable with the PAH that are present on diesel particles. Of course, DNA adducts were also found with carbon black exposed animals raising serious

questions about the cause and mechanism of formation of the adducts.

A recent review by the International Programme for Chemical Safety on health effects of diesel exhaust had an excellent summary table showing the concentrations of PAH on diesel exhaust particles. This table has been forwarded to the Agency. The relevant references are :

Scheepers, P.T.J. and Bos, R.P., (1992) Combustion of diesel fuel from a toxicological perspective. II. Toxicity Int. Arch. Occup. Environ. Health 64:163-177

Westerholm, R., Alsber, T. and Strandell, M. (1986) Chemical analysis and biological testing of emissions from a heavy duty diesel truck with and without two different particle traps. Detroit, MI. Society of Automotive Engineers (Paper No. 860014).

Volkswagen AG (1989) Unregulated motor vehicle exhaust gas components, Wolfsburg, Volkswagen AG - Research and Development, pp. 1-128. This last article could be readily obtained from the local Volkswagen office right there in Ann Arbor.

Page 9-43, 9.7 - Since the method of calculation of the carcinogenic risk departs from the usual methods employed by the Agency and does not consider the chemical constituents of diesel exhaust, which were the major concern in earlier Agency evaluations, a much more

detailed and complete explanation of how the carcinogenic risk was calculated is needed. This explanation should address the reasons for selecting the particle basis and ignoring the carcinogenic chemicals and address the matter of the selection of the linear model in the face of a nonlinear physiological process and nonlinear animal carcinogenicity data.

Page 9-46, PM_{10} - While the matter of particle standards is an important one, its discussion needs to be clearly related to the contribution of diesel exhaust to the total particle load. In general, the fraction of the total particle attributable to diesel exhaust is 10 to 15 percent.
If one examines the values of diesel particles in most environments of 1 or a few $\mu g.m^3$, this is only a very small fraction of the present NAAQS of 150 $\mu g/m^3$. Some statements need to be included to define the fraction of diesel particles in the total particle load.

10.0 GASOLINE PARTICULATE MATTER

Since the data base to calculate a cancer risk assessment for gasoline particulate matter does not exist, it is scientifically inappropriate to advance such calculations. They are nothing more than guesses, and comparing them to the values calculated for diesel particles, they are clearly much too high. There is nothing wrong with saying that there are no data on which to make a risk calculation and, therefore none will be attempted. The penchant for the Agency to come up with risk number whether supportable or not only adds to the lack of credibility about the way the Agency does its risk assessments. Indeed, honesty in saying that no risk assessment will be calculated in this case because of the complete lack of any data would be a refreshing change.

11.3 Carcinogenicity of Gasoline Vapors and Unit Risk Assessments

Page 11-7, 11.3.1.2 - This section suggests that gasoline vapors might be less carcinogenic than the whole vaporized gasoline used in the animal bioassays. It is imperative in doing the evaluation to determine the exact relationship between human exposures and those used in the animal studies. The

reality is that humans are exposed to only a very small fraction of the total gasoline and this must be reflected in the analysis. To blindly apply the animal studies to the human situation without this adjustment is simply incorrect scientifically.

Page 11-7, 11.3.1.5 - The calculation of a unit risk for gasoline based on the kidney tumors in the rats is contrary to the EPA policy cited and referenced in 11.3.3.1. Moreover, the use of the mouse liver tumor information must be evaluated in terms of the significant tumor yield in the controls and the near absence of tumors in male mice. It seems that the calculation of a unit risk is inappropriate given the available information and should not have been done.

Page 11-12, 11.3.3.1 - There is a substantial body of very sound experimental information relating to the production of alpha$_{2u}$-globulin in rats and their essential absence in humans. The section must have those key references (the work of Swenberg and Lehman-McKeeman) included Page 8 Review of "EPA Motor Vehicle-Related Air Toxics Study"

along with a discussion of the issues, since this information is key to understanding the production of tumors in the rats by the whole aerosolized gasoline. The very short paragraph in the draft as it now exists is not appropriate given the central scientific importance of this issue in understanding the kidney tumors produced in rats by exposure to whole gasoline vapor.

The studies of Swenberg, Lehman-Mckeeman and others clearly show that the "$_{2:}$-globulin formed in rat kidney after exposure to whole gasoline vapor is species specific for the rat, and that humans make little if any similar proteins. Thus, the use of the rat carcinogenicity data for a cancer risk assessment is not appropriate, and it is my understanding that the Office of Environmental and Health Assessment of the Agency has also made that conclusion and has indicated that the rat kidney tumor data will not be used for human cancer risk assessments. Some key references by Lehman-McKeeman are:

Toxicol. Appl. Pharmacol. 99:250-259 (1989)
Toxicol. Appl. Pharmacol. 103:539-548 (1990)
Toxicol. Appl. Pharmacol. 112:214-221 (1992)
Toxicol. Appl. Pharmacol. 116:170-176 (1992).

The reviews by Swenberg (Envir. Health Persp. Suppl. 101 (Suppl. 6):39-44, 1993), Rodgers and Baetke (Envir. Health Persp. Suppl. 101 (Suppl. 6):45-52, 1993) and Flamm, W.G. and Lehman-McKeeman, L.D., Reg. Toxicol. Pharmacol., 13:70-86 (1991) are especially instructive.

Page 11-16, 11.3.3.5 - There are several more recent studies on cancer in refinery workers that should be referenced and discussed, with one by Poole et al. that should be included.

Wong, O., Harris, F. and Thomas J. Smith, Health effects of gasoline exposure. II. Mortality patterns of distribution workers in the United States. Envir. Health Persp. Suppl. 101 (Suppl. 6):63-76 (1993)

Rushton, L., A 39-year follow up of the U.K. oil refinery and distribution center studies: Results for kidney cancer and leukemia. Envir. Health Persp. Suppl. 101 (Suppl. 6):77-84 (1993)

Schnatter, A.R., Katz, A.M., Nicolich, M.J. and Thériault, G., A retrospective mortality study among Canadian petroleum marketing and distribution workers. Envir. Health Persp. Suppl. 101 (Suppl. 6):85-99 (1993)

Responses to issues raised by EPA in the work order.

Task 3 -- Cancer Health Effects

1. The comments on the unit risk estimates for each of the air toxics considered are presented in the specific comments section.

2. The recent review by the Health Effects Institute of mobile source air toxics in which the EPA played a significant role has not identified any additional chemicals emanating from motor vehicle exhausts that were of concern. One area that has not received much attention is the mutagenic volatile polycyclic hydrocarbons. The previous considerations by the Agency have assumed that exposure to potentially harmful polycyclic aromatic hydrocarbon comes exclusively from particle exposure. With the recent information developed by Schutzle and others, this is clearly an over simplification and some assessment should be made of the volatiles. Unfortunately, only mutagenic data are available, and no chronic animal studies have been done.

The second substance of potential concern is methanol, which is being used to a small degree along with gasoline as a motor fuel, and which may considerably increased use. At the present time, the exposure information on which to make a health risk assessment based on exposure due to motor vehicles is poor. The risk, if there is one, will be very likely neurological from methanol. A related issue is the significant increase in formaldehyde, if large amounts of methanol are used as motor vehicle fuels. It would be appropriate to begin to model the levels of formaldehyde that could be obtained with a number of scenarios of methanol use so that some assessment could be made of the possible toxicity of formaldehyde under these conditions. Under these scenarios, the likely effects will be noncancer ones on the nasal and pulmonary systems. Methanol causes blindness in humans at very high doses with the target being the optic nerve. Similar disruptions of ocular function have been observed at lower doses in rats. For a complete review of the issues surrounding the matter of methanol toxicity, the report by the Health Effects Institute "Automotive Methanol Vapors and Human Health" is still an excellent resource even though it is now somewhat dated. There is some evidence in humans (cited in the Health Effects Institute report) from Russian studies that are less than adequately described. Nonetheless, they do indicate that some neurological/behavioral problems are seen after methanol exposure at about 1 mg/m^3, a concentration that could be reached in garages and other locales should methanol be widely incorporated into motor vehicle fuels.

Another review that summarizes the issues relating to methanol exposures is:
Kavet, R. and Nauss, K.M., The toxicity of inhaled methanol vapors. Crit. Rev. Toxicol., 21:21-50 (1990.

3. The questions and reservations about several of the risk estimates, particularly for formaldehyde, butadiene, diesel particles and gasoline vapor have been discussed above under the specific comments. In a general sense, if one totals all the cancer risks for the 1995 reformulated fuel scenario, the number is 469 new cancers. One must seriously ask whether this minuscule number is worth all the many thousands of dollars that are going into these analyses. Certainly, this number of new cancers could never be detected and are hardly a public health concern. Moreover, if one removes the gasoline particle number, which is nothing more than a crude, uneducated guess and gasoline vapor number, which under the Agency's policy should not have been calculated as it was, the number is reduced to 353 new cancers. Further, it is almost certain that the butadiene exposure numbers are high, possibly by an order of magnitude. Since butadiene contributes inordinately to the total cancer risk since it is such a potent animal carcinogen in mice (but not rats), the number of new cancers due to butadiene exposure could

be a slow as 20 rather than 207. In summary, there appears to be absolutely no cause for a public health concern for cancer from exposure to motor vehicle exhaust, and it would seem that the Agency could use its resources more productively on matters on higher concern.

4. The major concern is methodology used in the unit risk for diesel particle exposure. The Agency should give serious thought to a number of scenarios and not omit one that includes a consideration of exposure to the potential chemical carcinogens on the particles which are known to elute and give rise to DNA adducts.

5. Major populations of concern for exposure to motor vehicle exhaust have been identified in other studies. They include public service workers who spend large segments of time at or near roadways. The risks to the majority of the population would be small to nonexistent, since exposure to exhaust emissions is minimal, even when riding in closed motor vehicles with air conditioning systems.

6. The additional studies that were recommended to the Agency for review were noted in the specific comments section.

Task 4 -- Noncancer Health Effects

1. The method of obtaining RfC and RfD have been under discussion and development by the Agency for a number of years. This methodology seems to be the best available, and with further refinement should applicable to motor vehicle exhaust components. The major drawback at the present time is the lack of data for some components and the lack of a way to use pharmacokinetic data in this area to allow a reliable calculation of RfC or RfD.
In the cancer risk assessment area, there has been considerable thought given to the importance of pharmacokinetics and tissue distribution of carcinogenic materials in the assessment of risk. Unfortunately, there are no comparable models for non-cancer toxicity end points. It is an area that requires some intensive research to develop some theoretical models for biological responses related to animal responses and to exposures in humans. The issues will be especially difficult because non-cancer endpoints are most often
physiologically based, thus having a threshold and often not a linear dose response. It is a research challenge that seems uniquely relevant for the Agency. An interesting alternative to RfC for developmental toxicity has been proposed by Ryan. (Ryan, L., The use of generalized estimating equations for risk assessment in developmental toxicity. Risk Analysis 12: 439-447, 1992).

2. Some concern has arisen about the use methy-t-butylether, which is now used in many areas of the country to improve the oxygenate level. Most of the reports seem to be case studies related to odor discomfort, headache and other similar, but subjective, measures of well being. The toxicology data that has been developed indicates no problem with respect to reproductive toxicity, mutagenicity or cancer. The most recent review I know is by Constantini, Envir. Health Persp. Suppl. 101 (Suppl. 6):151-160 (1993). For the latest information on the status of the

various testing programs, you should contact the Oxygenated Fuels Association in Washington, D.C. They can provide you with the latest results of the studies and plans for future work. The main additives besides methyl-t-butyl ether (MTBE) are ethyl-t-butyl ether (ETBE) and t-amylmethyl ether (TAME). It is my understanding that there may already be some work underway with TAME.

The issue relating to the potential increase in formaldehyde levels with a significant increase in methanol as a motor fuel will need to be followed.

3. No additional comments.

4. How is this different from item 2?

5. There is a significant research program underway by the Oxygenated Fuels Association on MTBE and other potential additives.

6. No additional comments.

Task 6 -- Risk Assessment

1. Review presented under specific comments in each section.

2. See #3.

3. The issue of communicating uncertainty in risk assessment calculations is a critical issue, which the Agency unfortunately has been woefully behind. Adam Finkel of Resources for the Future has written extensively on this subject, and the Agency could well take his views and procedures and consider implementing them to give those who need to use the risk assessments to make public health decisions some high level of understanding of just how uncertain the values really are. Dr. Adam Finkel of Resources for the Future has written quite elegantly on the subject of uncertainty in health risk assessment. His writings include methodologies to put in formal and mathematical terms some analyses about the magnitude of uncertainties in risk assessment. Some publications you may want to review are:

Finkel, A., Computing Uncertainty in Carcinogenic Potency: A Bootstrap Approach Incorporating Baysian Prior Information. Report to the Office of Policy Planning and Evaluation, U.S. Environmental Protection Agency, Washington, D.C. 1988

Finkel, A.M., Confronting Uncertainty in Risk Management: A Guide for Decision-Makers, Center for Risk Management, Resources for the Future, Washington, D.C., 1990.

Finkel, A.M. and Evans, J.S., Evaluating the benefit of uncertainty reduction in environmental health risk management, J. Air. Pollut. Cont. Assoc., 38:1380-1385 (1987).

A few other interesting references on uncertainty are:

Bogen, K.T. and Spear, R.C., Integrating uncertainty and interindividual variability in environmental risk assessment. Risk Analysis 7:427-436 (1987)

Morgan, M.G. and Henrion, M., Uncertainty: A Guide to Dealing with Uncertainty in Quantitative Risk and Policy Analysis. New York. Cambridge University Press, 1990.

Gaylor, D.W., Chen, J.J. and Sheehan, D.M., Uncertainty in cancer risk estimates. Risk Analysis 13:149-154 (1993).

4. Noted above in general comments and in specific comments for each chemical entitity.

5. As noted above, the Agency must decide from a policy point of view whether a few hundred additional cancer deaths, which could, in fact be none, is worth the enormous effort. Since all areas of the country are within the standards for nitrogen oxides, and the situation for carbon monoxide is improving considerably with the introduction of oxygenates in the motor fuels, it seems as if the only remaining uncertainty relates to ozone exposure. With the recently completed cancer bioassay showing

no increase in tumors even at levels higher than those ever likely to be experienced in the environment, the remaining major uncertainty about components of motor vehicle exhaust is the pulmonary toxicity of ozone. The other air toxics reviewed in the EPA study are not of a public health concern.

Final Review of "Motor Vehicle-Related Air Toxics Study"

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August 24, 1994

This review is limited to the exposure assessment aspects of this study, i.e., Task 2. The review comments will follow the order of Task Items indicated in the "Services to be Performed."

1. Adequacy and Appropriateness of HAPEM-MS Model

While the use of a model such as HAPEM-MS, which attempts to move beyond the use of fixed site concentrations as estimates of exposure, is a laudable first effort in assessing the health impact of exposure to air toxics from motor vehicles, this model clearly has many severe limitations which may render it inadequate for its intended use. Several of these shortcomings have been identified in the Motor Vehicle-Related Air Toxics Study (MVRATS) report and/or in the public review comments. The following is a summary of some of the most important problems, from my perspective.

On the bottom of p. 4-1 and top of 4-2 it is stated that the EPA Denver/Washington, DC personal exposure study for CO "showed very good correlation between (fixed) monitor values and ambient exposure for all groups except the top 10% of the exposed individuals." This appears to be at odds with the conclusions drawn by Akland et al., 1985, which is the major peer-reviewed paper from this study. The authors stated that "the ambient levels (i.e., fixed site concentrations) are explaining less than 10% of the variance of the personal exposures" and "overall, these analyses suggest that 1-h values reported by the nearest fixed-site monitor or group of fixed-site monitors do not provide a good means of predicting simultaneous PEM values." Furthermore, the most recent EPA Air Quality Criteria Document for CO (U.S. EPA, 1991) presents a number of regression analyses for the Denver/Washington data, mostly showing low values of R^2, and concludes that "the analyses discussed above suggest that individual PEM readings are not highly correlated with simultaneous fixed-site readings." The source of the discrepancy in conclusions may be due in part to the qualifications included in the MVRATS statement, i.e., the use of "ambient exposure" and the exclusion of individuals above the 90th percentile of the exposure distribution. The meaning of "ambient exposure" is undefined and unclear, but if it refers to exposures only in outdoor microenvironments, then at least 90% of all personal exposure time is being ignored. Likewise, deleting the top 10th percentile of the distribution ignores the very people who we ought to be most concerned about, and whose protection from adverse health effects should be the driving force of any new regulations.

The microenvironmental exposure factors given on p. 4-6 of the MVRATS report, used to convert fixed-site concentrations to microenvironmental concentrations, were apparently derived from the Denver data only. For a model purporting to be applicable to national exposure estimates, why wasn't at least the readily-available Washington data also included? A comparison or averaging with the Denver data would begin to address the question of generalizability. The use of such constant factors within and among widely varying urban and rural areas in diverse regions of the country needs to be justified. For instance, summertime residential cooling may employ recirculated refrigerated air in hot humid climates and evaporative cooling with high outdoor air infiltration rates in hot arid climates. The relationship of indoor levels of outdoor generated pollutants to fixed-site concentrations may be considerably different for these two situations. Likewise, factors such as proximity of indoor environments to roads, and density of traffic and status of windows (open or closed) while commuting inside a vehicle, would be expected to

significantly affect exposures in these microenvironments; however, these factors are totally unaccounted for in the model.

The assumption that CO is a reasonable surrogate for various air toxics emitted from motor vehicles is highly suspect. The authors of the report admit that this assumption is not valid for "more reactive pollutants." Presumably this would include such target compounds as 1,3-butadiene, formaldehyde and acetaldehyde, as well as many others. Given this rather obvious problem, there is a need to demonstrate the reasonableness of using CO as a surrogate for some relatively stable toxic. Of the toxic pollutants specifically addressed in the MVRATS report, only benzene appears to fulfill this requirement. The report indicates that benzene is considered quite stable in the atmosphere, with relatively long residence times. Empirical data from two studies can be used to examine the relationship between in-vehicle concentrations of benzene and CO, and the relationship of each to fixed-site concentrations. The study performed in Southern California (Shikiya et al., 1989) showed that the mean in-vehicle concentrations of both CO and benzene were more than twice the corresponding fixed-site levels. Although simultaneous measurements of both pollutants were made in the vehicles, no correlations were reported. The study performed in Raleigh, NC (Chan et al., 1991) showed that median in-vehicle concentrations of CO and benzene were four and seven times greater, respectively, than the corresponding fixed site concentrations. Moreover, the correlation coefficient for the CO and benzene in-vehicle concentrations was less than 0.5, similar to that found for several other VOCs. The investigators concluded that "the extrapolation of CO commuter exposure models to the study of commuters' VOC exposures would be ill-advised." These results clearly do not support the assumptions of the HAPEM-MS model, nor do they agree with the microenvironmental factor of 1.554 for inside motor vehicles. Additional questions can be raised about the use of a gaseous compound, CO, as a surrogate for diesel and gasoline particulate matter. Clearly, the validity of these assumptions must be demonstrated.

The derivation of the integrated exposure adjustment factor for the motor vehicle-related ambient levels (presented in Chapter 5, instead of Chapter 4 where it belongs) is based on a California activity study. Why were the Cincinnati data not used here? Do the modelers consider California activity data to be representative of the nation as a whole? Why not attempt to integrate the results from a number of studies that have reported activity data in order to obtain the best national estimate? It should also be pointed out that the derivation of this factor equates time "at work" with the microenvironment "indoors-other." Of course there are many instances where these are not equivalent, resulting in serious misclassification, e.g., working outdoors or shopping in a mall.

2. Adequacy of Source Apportionment

Verification of the specific percentages of ambient levels of individual toxic pollutants attributable to motor vehicle sources is somewhat beyond my expertise. The general procedures used to derive these apportionments seem reasonable, based on the data utilized. However, once again, the utility of employing a single estimate for the entire country is questionable. For example, the relative apportionment of mobile and major point sources of benzene should be quite different for Houston and Washington, DC.

3. Atmospheric Transformation

I cannot adequately address this issue; it is outside my area of expertise.

4. Comparison of HAPEM-MS Exposures to Ambient Monitoring Data

The comparison of annual average exposures predicted by the HAPEM-MS model with mean ambient levels adjusted for motor vehicle contribution and integrated exposure is a gross test of model performance. Even this rather insensitive evaluation indicates significant differences between model output and adjusted ambient data for all pollutants except for benzene. This is consistent with the known and suspected limitations of the model. Given these limitations, and until a more realistic model is developed, the "correction" of the modelled exposures to agree with the adjusted ambient data seems justified. It is not known how "reasonable" these final exposure estimates are, especially if the entire distribution of exposures is considered. Proper validation of the model would be required before this could be ascertained.

5. Uncertainties of Exposure Estimates

The uncertainties associated with the final exposures estimates are unknown, and probably enormous for the highest percentiles of the exposure distribution, given the limitations outlined here and in the study report. One way to evaluate the current model would be to perform a sensitivity analysis, whereby reasonable ranges of model parameters are substituted in the model in order to ascertain the relative influence on model output. This would provide some feeling for how stable the model estimates are. However, the best way to address uncertainty is to perform a full-scale validation of the model, or essential parts of it, by comparing model output with accurate empirical data. A number of well-designed personal monitoring studies in different areas of the country would be necessary to adequately evaluate the assumptions and parameters employed in the model. This would undoubtedly result in a revised and more realistic exposure model.

6. Short-Term Microenvironment Exposures

The various pollutant-specific sections on short-term microenvironment exposures are not very enlightening, due to the absence of sufficient data to investigate a link with short-term health effects. However, the data presented can be used to test and improve the HAPEM-MS model. For instance, in-vehicle exposures are usually repetitive exposures in an important microenvironment that may contribute substantially to integrated personal exposures.

7. Alternate Approaches to Estimating Exposure

An alternate approach could begin by validating and improving the current model, as discussed earlier. Elements of other existing relevant models (Rosenbaum and Anderson, 1993; Behar et al., 1993) can be used to incorporate known important determinants of exposure to toxic pollutants. Additional field studies of personal exposure to toxics will be needed to provide data for model improvement.

8. Exposure Data for Noncancer Health Risks

The quantification of noncancer health risks from exposure to air toxics will undoubtedly be a major challenge for future risk assessments. The kinds of exposure data required, short-term or long-term, depends on whether we are trying to assess acute effects, such as exacerbation of asthma and sensory irritation, or more chronic effects, such as respiratory disease and immunological, reproductive and developmental disorders. In either case, much more monitoring data is required exploring the relationships among ambient, microenvironmental and personal exposure to air toxics. At this point in time there are certainly insufficient data for any toxic compound.

9. Additional References

Literature references cited in the previous Task Items that are not already cited in the MVRATS report, or are not self-explanatory (1991 CO Criteria Document) are given below:

Available at the time of the study

C.C. Chan et al., "Driver Exposure to Volatile Organic Compounds, CO, Ozone, and NO_2 under Different Driving Conditions," *Environ. Sci. Technol.* **25:** 964-972 (1991).
(Note: an earlier, nonpeer-reviewed conference paper was cited for this study in Chapt. 5)

Available subsequent to the report

A.S. Rosenbaum and G.E. Anderson, "Modeling of Indoor and Outdoor Exposures and Risk from Outdoor Benzene Emissions in Los Angeles," In: *Modeling of Indoor Air Quality and Exposure*, N.L. Nagda, Ed., STP 1205, ASTM, Philadelphia, PA, 1993, pp. 257-270.

J.V. Behar et al., "Modeling of Human Exposure/Dose to Benzene," *ibid.*, pp. 280-290.

Ongoing work

Since metals and VOCs are target pollutant categories for the national exposure surveys being planned for the NHEXAS program, data from these efforts may be useful in the future.

Comments on Chapter 9
U.S. EPA Motor Vehicle-Related Air Toxics Study

U.S. EPA Office of Mobile Sources
Ann Arbor, Michigan, April 1993

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SUMMARY

The study prepared an extensive review of Diesel exhaust risk- related activities and substantially improved the estimates of national emissions and public exposures for assessing Diesel engine emissions. The analysis concluded with a preliminary estimate that the U.S. nationwide annual average exposures were at the level of 1.8 ug Diesel particles/m3 in 1990 and will decline by 78% in the next two decades. When continuous 70 yr.-long exposures to these levels were assumed and their effects projected for the U.S. population (using the EPA 1991 unit risk determined from animal data), the study estimated that the annual lung cancer excess due to Diesel emissions was in 1990 at the level of approximately one hundred deaths for 190 million U.S. urban residents (i.e. approximately 0.1 % of all U.S. lung cancer deaths and one in two million lung cancer death risk for U.S. urban population). The study also predicted that within twenty years, the excess deaths will decline due to existing and already mandated emission restrictions by 75% in spite of significantly increased vehicle miles traveled.

The estimated exposure levels are lower than those reported in previous assessments and their reality and quality supersedes similar attempts by Federal and State authorities. The expected health effects of Diesel exposures may be further reduced when recent discoveries clarifying Diesel particle effects are considered. New experimental data profoundly modify mechanisms of Diesel particle actions, establish a distinct no-effect level (threshold), exclude an automatic application of linear multistage models and may result in much lower estimates of Diesel-induced health effects after the information is incorporated into EPA's risk assessment guidelines and Diesel health assessment document. These facts suggest that the lung cancer risk of Diesel emissions for U.S. residents is and will remain at a level that is low and indistinguishable from the background cancer risk.

INTRODUCTION

The study was conducted pursuant to Section 202(1)(1) of the Clean Air Act (as amended in 1990) to answer the question whether or not "the need exists for, and what is the feasibility of, controlling emissions of so far unregulated toxic air pollutants that are associated with

motor vehicles and motor vehicle fuels". While the study is in general focused on those categories of emissions that pose the greatest risk to human health, or about which significant uncertainties remain, it evaluates emissions from all types of automobile exhaust including Diesel engines.

In evaluating the cancer health effects of Diesel emissions, the study uses two working hypotheses assuming that:
(a) a cumulative exposure (such as occurring in controlled animal experiments) provides an adequate basis for concluding that the resulting accumulation of the chemical in the body is the primary factor for the resulting tumor-producing effects;
(b) that the animal-derived unit risk can be linearly scaled to human populations using a simplified approximation that this unit risk multiplied by an estimated annual exposure realistically approximates the excess incidence of Diesel-induced lung cancer deaths in the United States.

The estimated carcinogenic risks from Diesel particles are based on the "now under revision and subject to change" EPA 1991-derived unit risk. The study concludes with a predicted annual excess of 109 cancer deaths in 1990 and a projected decline by approximately 75% in 2010.

Limitations of the used approaches are listed on page ES43-ES46 and indicate that the cancer risks are not meant to be representative of "actual risk" but should be used in a relative sense "to compare risks among pollutants and scenarios and to assess trends".

REVIEW COMMENTS

This review provides comments on:
(1) exposure estimation and Diesel exposure model (Sec. 9.3 & 9.5);
(2) feasibility of the use of polycyclic organic matter (POM) as the mechanisms of Diesel particle-induced effects (Sec. 9.4);
(3) chemical carcinogenicity of Diesel Particles and the reality of the risk estimates (Sec 9.6).

Concerns about non-carcinogenic effects of Diesel particulate matter (Sec. 9.8) are based on animal-established no-observable-adverse-effect level (NOAEL). These concentrations exceed ambient levels by two orders of magnitude, and are - in the view of the reviewer - important for occupational hazards but irrelevant to ambient exposures. The alleged daily mortality effects of fine particles (page 9.46-48) require further analyses before they are applied in the regulatory process.

1. Emissions (Sec. 9.3) and Exposure Estimation (Sec. 9.5)

The EPA's team of authors should be congratulated for an excellent engineering analysis of the problem and for the included correction factors that significantly improve the credibility of the proposed estimates. In this respect, the EPA's analysis provides substantially improved emission estimates that supersedes other analyses by Federal (EPA, 1987) or other governmental agencies (CARB, 1994).

The question, however, remains whether or not even this improved analysis represents the actual Diesel contribution to the total mass of fine particles in the ambient air and whether or not the calculated ambient levels accurately reflect the probability of experiencing an inhalation contact with these levels for U.S residents.

The improvement in emission estimates is mainly achieved by using an approach proposed by Sienicki et al. (1991). The EPA authors accepted Sienicki's 1995 lower emission factors (EF) caused by stricter standards, lower light duty market shares and low sulfur fuel but did not include freeway road adjustments. The authors do not explain why the freeway road correction was not used. The text should list technical reasons for this decision rather than to refer to "past EPA practice" (page 9-9). As a result, the EPA's 1995 emission rates of 0.0356 g/mi are larger than Sienicki's estimates of 0.0305 g/mi. This may lead to a potential overestimate by approximately 17% in the urban fleet averages.

Instead, the authors use a Mobile 4.1-derived vehicle-miles- traveled split to correct for the use of heavy duty subclasses in rural environment and arrive at a level of 0.0523 g/mi for the 1995 year. This overestimates the Sienicki's value by approximately 71%. The text should indicate that no specific method exists today that would determine the actual Diesel particle contribution to the total mass of TSP or PM10 and validate the applicability of these adjustments. In Section (9.5.2), the HAPEM exposures are compared with the contribution of Diesel particles estimated from monitoring data on total suspended particulates (TSP). The results need to be corrected because the estimate used for Diesel emissions of 384,000 metric tons/year sharply contrasts with a more appropriate estimate of 163,118 metric tons listed in preceding text (Section 9.3.3 and Table 9-3, page 9-10). When the lower estimate is used in calculating Diesel contribution to TSP, the correct contribution will not be 5.12 % but 2.17% and the resultant ambient concentration 1.04 ug/m3 instead of 2.46 ug/m3. If adjusted for the "integrated exposure" (using an empirical correction factor of 0.62 listed on page 5-29 that adjusts 24-hr. ambient levels to account for generalized activity patterns and microenvironmental factors), the resulting "integrated" exposure estimate is 0.64 ug/m3 instead of 1.52 ug/m3. Again this represents a 236% overestimate. When the 1990 HAPEM-MS urban estimates are compared with this value, the proposed level of 2.03 ug/m3 equals to 316 % of this value, and the rural estimate of 1.1 ug/m3 represents a 171% overestimate).

Table 1. Differences in the Projected Ambient Contribution and Levels of Diesel Particulate Matter

Diesel Contribution:	1990 HAPEM Estimate	1990 TSP-Derived original	1990 TSP-Derived adjusted	1990 PM10-derived
Diesel Fraction of Ambient Particles	--	5.12%	2.17%	2.9%
Projected Levels:				
urban integrated % HAPEM overestimate	-- 2.03	2.46 ug/m3 1.52 ug/m3 134%	1.04 ug/m3 0.64 ug/m3 236%	0.93 ug/m3 0.57 ug/m3 356%
rural % HAPEM overestimate	1.1 ug/m3	1.52 ug/m3 73%	0.64 ug/m3 175%	0.57 ug/m3 193%
nationwide % HAPEM overestimate	1.8 ug/m3	1.52 ug/m3 118%	0.64 ug/m3 281%	0.57 ug/m3 316%

Because of the submicron size of Diesel particle, it would be even more appropriate to use fine particles (PM-10) rather than the total suspended particulates. If PM-10 data are applied, the differences would be also large. The 1990 mean annual PM-10 concentration was approximately 32 ug/m3 and the contribution of highway vehicles was estimated at the level of 1.48 milion short tons (1.34 million metric tons) out of 50.85 million short tons (46.12 million metric tons) per year (2.9%) in 1990 (U.S. EPA, 1992). The contribution of all highway vehicles (when used as the worst case surrogate for Diesel fleet) to ambient levels would then be a national average of 0.93 ug/ m3. When adjusted for the "integrated exposure" (0.57 ug/m3), these estimates represent approximately one quarter of levels reported in the text. This indicates a considerable level of variability (73 to 356%) in the proposed ambient levels. If the freeway road adjustment were used, the uncertainties would be even greater. Moreover, the apparent consistency among the TSP- and PM-10-derived estimates further supports the notion that the HAPEM levels may be substantially overestimated (Table 1).

In the light of the unusually large uncertainty in predicting ambient levels, the accuracy of the proposed values characterized by three valid digits is exaggerated. The uncertainty may be further augmented by the fact that the used HAPEM method is based on human activity patterns from only one city and may not represent intercity differences. The use of rounded values would be

more appropriate.

Moreover, the actual Diesel-induced effects are governed more by the experienced peak concentrations in individual microenvironments than by an integrated exposure. Considering that people spent most time indoors, i.e. an environment with different composition of fine particles than outdoors, the HAPEM method may need to be replaced by recent stochastic estimates that would weight peak concentrations in specific microenvironments more than the integrated exposure. Probabilistic approaches have been successfully applied to other pollutants, e.g. ozone and dramatically improved the accuracy of population exposure estimates (Johnson et al., 1992,1994, McCurdy et al., 1994a,b, Vostal et al., 1993). Similar methodology can be easily applied to fine particles and substantially enhance the credibility of the risk assessment process. Limitations of the HAPEM methodology listed on page 4-7 to 4.8 suggest that further improvements of actual exposure estimates would remove a significant amount of the existing uncertainties.

2. Atmospheric Reactivity and Residence Times of Particulate Phase Polycyclic Organic Matter (Sec. 9.4)

The text presents this issue as an important public health risk. However, it should be emphasized that this discussion does not belong in a chapter analyzing potential effect of Diesel particles because the polycyclic organic matter (POM) category:

(1) consists of undefined and highly variable mixtures of unknown components;
(2) has a hypothetical character and its actual role has never been validated;
(3) represents no health-specific index of air pollution; and
(4) its biological potency when expressed by speculative surrogates (such as benzo(a)pyrene) is arbitrary and unjustified.

Its inclusion raises substantial doubts about the reality of the risk estimates (Leonard, 1992).

Historically, several industry, government and academic laboratories tested ambient and Diesel engine-derived particles for potential effects on public health in the late 1970's. The studies revealed that Diesel particles consist of a carbonaceous core with variable amounts of adsorbed chemical on their surface. This material can be separated (extracted) from the core by elaborate chemical procedures at temperatures incompatible with the human body environment and by using industrial solvents that do not exist in living organisms. Because some of these extracts contained traces of chemicals with mutagenic effects in microbial assays, the U.S. EPA Office of Research and Development issued a precautionary notice on laboratory handling of exhaust products from Diesel engines. The warning recommended that standard

laboratory procedures for handling "potentially hazardous material" be used until additional data are developed.

Unfortunately, the warning was based on an incorrect assumption that the "mutagenicity assay has been shown to be 85% to 90% accurate in detecting substances that are carcinogenic in whole animal studies" (U.S. EPA/ORD, 1977) believed at that time. The 1970's concepts originated from experimental observations that a large number of carcinogens are mutagenic in bacteria, thus leading to a conclusion that "mutagens are carcinogens"(Ames, 1979). However, recent data show that a high percentage of the natural or synthetic animal carcinogens identified by chronical testing at the maximum tolerated dose "are non mutagens" (Ames and Gold, 1990a,b, Ames et al., 1990). These observations seriously question the role of genotoxicity as the sole mechanism of carcinogenesis (Ames and Gold, 1990a), but speculative deductions on the carcinogenic action of the solvent extracts led to an extensive testing of ambient particles (Lewtas, 1983) and premature conclusions on the role of "products of incomplete combustion (PIC)" in human and animal carcinogenesis (Lewtas et al., 1987). Moreover, the concept was introduced into an analysis of the air toxics problem in the United States (U.S. EPA/OPPE, 1985). The authors first concluded that motor vehicles were responsible for about 20% of the air toxics risk. When the category of "products of incomplete combustion (PIC)" was introduced into the assessment process, the same report raised the risk attributable to motor vehicles to nearly 60%.

Continuing promotion of the PIC- and POM-induced lung cancer concept further confused the question of air pollution-associated urban incidence of lung cancer (Lewtas et al., 1990, Lewtas, 1991), particularly after negative data on bioavailability of particle-associated polycyclic organic matter and specific DNA adduct formation have undermined the credibility of these predictions for Diesel exposures. The use of PIC- or POM-related categories as an index of adversity of air pollution was repeatedly criticized and their inclusion into risk assessment methodology was seriously questioned (Leonard, 1992). Because of these uncertainties, the inclusion of Section 9.4 discussing the "polycyclic organic matter" unnecessarily clouds the issue and is irrelevant to Diesel action.

3. Carcinogenicity of Diesel Particles and Unit Risk Estimates

(a) Animal Data

The text starts with a caveat that the information contained in this section on chemical carcinogenicity of Diesel particles has been taken from a preliminary draft of the Diesel health assessment document prepared by EPA in 1990 (U.S.EPA, 1990). However, the text fails to inform the reader that the draft was criticized and is now in the process of being revised totake into account public comments and new scientific information.

Most criticism of the draft came from the fact that the traditional

concepts of EPA's risk assessment process failed to consider experimental data that opposed genotoxic mechanisms of Diesel particles. Mainly, the assessments ignored early pharmacokinetic data that showed the inappropriateness of an automatic application of findings obtained by artificial extracts or by procedures that are incompatible with the biological environment.

First, these studies demonstrated that the mutagenic activity of Diesel particles was: (1) minimal or negative when tested in extracts obtained with biological fluids; (2) substantially dependent on the presence of high levels of nitroreductase enzymes that are not present in mammalian cells; and (3) disappeared completely 48 hours after Diesel particles had been phagocytized by alveolar macrophages. In addition, long-term animal exposures to Diesel particles did not induce the activity of hydrocarbon-metabolizing enzymes or specific adverse immune responses - as it would be expected if the particle-adsorbed chemicals were involved in Diesel action - unless solvent extracts of diesel particles were directly administered to animals in doses that highly exceed the levels of public exposures. (Vostal, 1980, 1983, Chen, 1981, Chan, 1984, etc.)

Instead, more realistic explanation of Diesel carcinogenicity has been replaced by speculative predictions based on short-term mutagenicity tests which included projections on Diesel-induced annual lung cancer incidence (Albert et al., 1983). In fact, continuing emphasis on the genotoxic concepts misdirected the general attention into an erroneous identification of nitroaromatic hydrocarbons as the major component responsible for the tumor-producing effects of high Diesel concentrations. The mistaken concepts on the role of nitroarene-containing extracts influenced

other advisory agencies and their assessment of carcinogenic risks (IARC, 1989).

More importantly, the alleged effects of the extractable mutagenic fraction of Diesel particles were seriously challenged when formation of animal lung tumors after high loads of Diesel particles was reported in 1983 (Ishinishi, 1986). Alternative mechanisms compatible with epigenetic (non-genotoxic) character of the produced animal tumors were proposed (Vostal, 1986). This criticism was further endorsed by new animal studies (Heinrich et al., 1992, Mauderly et al., 1991, Nikula et al., 1991 and 1992). Finally, the U.S. EPA recognized in 1991 that "neither the vapor phase of Diesel exhaust or the particle-adsorbed organic fraction are responsible" but that the "tumor response noted in animals could be accounted for by a particle effect alone" (Pepelko et al., 1991).

These new discoveries considerably modify the interpretation of the carcinogenic effects of Diesel particles and will probably become the scientific basis for the new draft of the EPA's health assessment document. The animal studies reaffirm non-genotoxic mechanism of Diesel action by showing that no differences can be found in the character and number of lung tumors between Diesel- , carbon black- and titanium dioxide-exposed animals. The first study reports that the animal experiments provide "no evidence for a Diesel-particle-specific carcinogenic action but demonstrate a general particle-produced carcinogenic effect" (Heinrich et al., 1992). The results of the second study reassure that the "high lung burden of carbonaceous particles is the principal cause for the increased prevalence of lung neoplasms in rats exposed to high concentrations of Diesel exhaust". The soot-associated organic compounds do not appear to contribute significantly to the prevalence of neoplasms in the animal assay and "do not support the estimation of human lung cancer risk from rat data on the basis of the particle-associated organic compounds" (Mauderly et al., 1991, Nikula et al., 1991 and 1992). Any new assessment of the potential public health risk of Diesel particles - including the present study - should, therefore, include these data in the final interpretation of Diesel exhaust action (Vostal, 1994a). References to these findings should not only appear in the text of this chapter but new information should be also reflected in a discussion of how these new data modify the entire risk assessment process.

Second, non-genotoxic mechanisms - when accepted as a plausible explanation of the Diesel particle action - introduce an unquestionable existence of no-effect levels for the "carcinogenicity" of Diesel exhaust observed in animals (Vostal, 1994b).

It has been repeatedly argued that the mathematical dose-response function for chemical (genotoxic) carcinogenicity is linear or is "unlikely to exceed linearity" in the low dose region because of the probability that even one single chemical molecule can initiate a mutagenic event that leads to uncontrolled cell division and cancer. In contrast, the epigenetic action implies that a distinct amount of the agent or effects accumulates before the tumor-producing effect starts. This shows a non-linear function in the dose response curve with an established threshold. While no dependable mathematical model exists at this time for this function in the low-dose region, the non-linearity applies even when Diesel particles are considered as a potential promotor in an already initiated genotoxic process (Pepelko et al., 1994). All major components of the possible promoting action i.e. physical irritation, inflammation or fibrotic action are typical threshold-displaying processes and their action cannot be linearly extrapolated to low doses.

Fig. 1 The Relationship between the Predicted Soot Deposits in the Lung and the Frequency of Tumors in Inhalation Studies (from Vostal, J.J., 1986)

Theoretically, a linear function of an epigenetic process can be assumed for the dose response curve after the no-effect intercept has been exceeded. While experimental data suggest linearity of tumor responses after excessive amounts of Diesel particles accumulated in the lung (Vostal, 1986 - Fig. 1), the approach is not suitable for predicting effects at low ambient levels. The epigenetic mechanism restricts, therefore, the applicability of the linear dose response model for ambient concentrations and attempts to do so have been

appropriately criticized.

(b) Human Data

In discussing human epidemiology data, the document correctly identifies the lack of data on the actual diesel exhaust exposure as the major deficiency of all studies. In addition, the undocumented smoking habits, other present or previous occupational exposures and potential job misclassification as well as inadequate characterization of the population, etc. are critical confounding factors that are not always removed by statistical adjustments and do not permit more definitive linking of the Diesel exhaust to the specific effect in question (i.e. lung cancer). These characteristics of epidemiologic approaches limit a unique identification of Diesel exposures as a causal factor in practically all published studies. In addition, seven listed bladder cancer studies should be eliminated from the evidence since they refer to a different health endpoint and are irrelevant for the purpose of this analysis.

Considering the "most convincing" study by Garshick et al. (1989) study, it should be recognized that this study also fails to provide a documented exposure because the analysis is based on "reconstructed" exposure levels. It is even more surprising that the U.S. EPA study does not include references to a critical reanalysis conducted by Crump and Chen (U.S. EPA contract 68-02-4601, Assignment # 182) that identified numerous limitations in the Garshick study, detected a significant number of unrecorded deaths that must have occurred in the cohort after 1977 and conducted more than 50 analyses of the relationship between the alleged exposure to Diesel exhaust and lung cancer mortality. None of these analyses showed a pattern that was "consistent with an adverse effect of Diesel upon lung cancer; in fact, many of them showed a statistically significant negative association" (Crump et al, 1991). Obviously, the Garschick et al. study suffers from the same confounding factors that have been criticized in other analyses.

Because documented exposure is an absolutely required factor for the dose-response curve, the text should conclude that until additional (prospective) studies provide more adequate documentation of exposure, the use of epidemiology data in the risk assessment process remains questionable. At this time, the conclusion that the data are inadequate for quantitative risk assessment is fully justified.

CONCLUSIONS

In general, the study presents an excellent summary of what is known and what has been published on different approaches in the assessment of potential carcinogenicity of Diesel particulate matter.

First, the document introduced into exposure estimates a substantial improvement over previous reports. The engineering analysis prepared by the professional staff of the Office of Mobile Sources has much higher validity than similar attempts by other State or Federal agencies. The professional staff of the Office of Mobile Sources should be commended for a job well done.

On the other hand, in spite of these improvements the study should explicitly recognize that significant level of uncertainty exists in the methodology estimating actual exposure levels in the U.S. residents. The text should, therefore, particularly emphasize the high level of uncertainty existing in the exposure as well as the biological action estimates. In addition, calculated values are often presented by three valid digits and leave a false impression of accuracy. More rounded values would be appropriate. Similarly, the final estimates should not be presented by a single number, but - wherever possible - also by statistical variances. If a statistical variance is not applicable, the approaches can be organized in the form of one or more probability distributions and by summary statistics computed through Monte Carlo analysis or other probabilistic analysis techniques. These iterative approaches will not only improve the scientific accuracy of the estimates but will also indicate the level of uncertainty by more descriptive zero-to-upper-bound ranges- even if they start at or below zero. Only after the probability distributions and the level of uncertainty are incorporated into all reported values, will the Congress, the decision maker or the public have an adequate information on the reality of projected effects. In fact, the limitations and characteristics of the assessment listed on page ES-43 should be repeated with all Tables and conclusions.

Second, the study would also benefit from providing more updated information and alternative interpretations of the carcinogenic action of Diesel exhaust. The text should particularly recognize that - in contrast with the prevailing concepts - new findings unequivocally reject the theory of chemical carcinogenicity assumed for Diesel particles on the basis of microbial testing of particle extracts. While we do not understand exact mechanisms responsible for the formation of tumors in laboratory animals, new data characterize the tumor-producing action of high Diesel exposures as a non-specific, epigenetic mechanism produced by the presence of accumulated foreign material (particle depots) on a terrain modified by inflammatory and degenerative processes (U.S. EPA, 1993).

These findings have already been accepted by U.S. EPA assessors who

acknowledged that "the weight of evidence favors basing risk assessment on the lung burden of particulate matter rather than particle-adsorbed organics or vapor phase components" (Pepelko et al., 1992). The document would significantly benefit if the new information is not only reflected in the text but is actively used in the assessment process.

If some of these limitations were caused by the fact that a new draft of the EPA's health assessment document has not yet been released, the authors should keep in mind that the Congress- mandated analysis ".. shall accurately reflect the latest (emphasis added) scientific knowledge useful in indicating the kind and extent of all identifiable effects on public health or welfare .. " (CAA 1977, Sec. 108(a)(2)).

In conclusion, the chapter is an excellent progress report on the continuing efforts to correctly assess the potential public health impact of Diesel emissions. It also provides significant improvements in the evaluation of the Diesel-induced exposures and risks. Hopefully, a further improved version of the assessment can be expected in the near future. Until that time, the study suggests that the lung cancer risk of Diesel emissions for U.S. residents is at a level that is low and indistinguishable from the background cancer risk - if existing et all - even if the estimated cancer risks "are not meant to be representative of actual risks" (page ES-43).

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Comments on the Risk Assessment Approaches U.S. EPA Motor Vehicle-Related Air Toxics Study

U.S. EPA Office of Mobile Sources
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SUMMARY

The Motor Vehicle-Related Air Toxics Study assesses carcinogenicity of benzene, formaldehyde, 1,3-butadiene, acetaldehyde and Diesel particulate matter released through emissions from mobile sources by using potency estimates that were developed by the EPA's Office of Health Assessment under the "default" risk assessment process in the 1980's. Although the EPA report did not estimate total cancer risk due to uncertainties associated with additivity of cancer risk, the analysis projects an excess of 580 cancer cases per 250 mill. U.S. residents (2.3 cases per million) in 1990 due to benzene, formaldehyde, 1,3-butadiene, Diesel and acetaldehyde alone. This excess will be reduced by 50% within the next two decades because of the existing or on record regulations and in spite of the increased number of registered vehicles and vehicle miles traveled.

The review points out that the results of the study are based on potency estimates and risk assessment methodology that were developed on information available in the 1970's and emphasizes advances that occurred in the understanding of the carcinogenic process since that time.

If - contrary to the current EPA's risk assessment approach - cancer mechanisms other than direct chemical damage to DNA prevail and if a no-effect threshold exists for these epigenetic mechanims, the use of a "default" risk assessment process that assumes a linear low-dose extrapolation for all chemical carcinogens regardless of the real mechanism of their action is unjustified and may result in a serious overstatement of risks that do not exist. Introducing iterative approaches proposed by the recent NAS report into the assessment methodology would significantly improve the quantification of uncertainties inherent to the assessment process. More importantly, using potency estimates developed under EPA's new guidelines (now in review process) will further reduce the estimated public health risks of air toxics from mobile sources and may demonstrate that the effects cannot be differentiated from other everyday life risks.

The Motor Vehicle-Related Air Toxics Study has been completed but the necessity of upgrading the assessment process on the basis of more current science and EPA's new carcinogenicity guidelines should be seriously considered before the results are used in risk management decisions and the final rulemaking process. Otherwise, unnecessary regulations will impose cost on society that would not convey corresponding benefits in terms of health protection.

INTRODUCTION

The study was conducted pursuant to Section 202(1)(1) of the Clean Air

Act (as amended in 1990) to answer the question whether or not "the need exists for, and what is the feasibility of, controlling emissions of so far unregulated toxic air pollutants that are associated with motor vehicles and motor vehicle fuels". While the study is focused on those categories of emissions that pose the greatest risk to human health, or about which significant uncertainties remain, it evaluates emissions from all types of automobile exhaust. The study summarizes what is known about motor vehicle-related air toxics with the intention "to present all significant scientific opinion on each issue".

The report quantitatively assesses carcinogenicity of benzene, formaldehyde, 1,3-butadiene, acetaldehyde and Diesel particulate matter by using potency estimates that were developed by the EPA's Office of Health Assessment in the 1980's. When considering the remaining air toxics, such as the gasoline particulate matter, gasoline vapor et al. the authors declare that these estimates are overly "conservative and more highly uncertain than the risk estimates for the other pollutants examined in this study." The estimates are called "pro forma values" and are not included in the summary of cancer/death incidence due to motor vehicles. While the Agency avoided developing an estimate of total cancer cases due to uncertainties in the additivity of cancer risks, the analysis projects an excess of 580 cancer cases per 250 mill. U.S. residents (2.3 cases per million) in 1990 due to benzene, formaldehyde, 1,3-butadiene, Diesel and acetaldehyde alone. This excess will be reduced by 50% within the next two decades because of the existing or on record regulations and in spite of the increased number of registered vehicles and vehicle miles traveled.

Limitations listed on page ES-43 point out uncertainties in the used potency, emission and exposure estimates. Thus, the cancer risk estimates "are not meant to be representative of actual risk. Instead, they are meant to be used in a relative sense to compare risks among pollutants and scenarios and to assess trends." Because cancer risks estimates are based on upper bound estimates of unit risk (except benzene) using animal data, "point estimates were reported rather than a range that would accurately bound the estimates. The true risk could be, therefore, as low as zero or fall above the point estimates" (U.S. EPA, 1993a).

The authors recognize the need to address these uncertainties but do not explicitly account for weaknesses introduced by the unit risks that have been changing with the advanced research. For formal reasons, the study used only EPA-released unit risks in spite of the fact that many of them were based on information obtained in 1970's. The Agency is conducting its peer review subsequent to completion of the final document. Comments made by peer reviewers will not be used to revise the study but will be considered during the rulemaking process.

REVIEW COMMENTS:
The review focuses on the EPA's overall approach to assessing carcinogenic risks from motor-vehicle-related air toxics, alternative approaches that may be considered, the inherent uncertainties in the

assessment process, what is the likely impact of alternative methodologies on the conclusions of the study and the way these uncertainties are communicated to the readership.

A. EPA's Overall Approach

A realistic assessment of cancer risks from exposures to ambient air toxics depends on best available information on:

(a) the inhaled ambient concentrations;
(b) the number of people that are exposed to these concentrations and
(c) the carcinogenic potency of the chemical compound in question.

The Motor Vehicle-Related Air Toxics study effectively resolved the first two tasks by developing innovative approaches and using previously unavailable data. The authors deserve a full credit for substantially improving the exposure part of the equation.

The outcome of the assessment is, however, limited by the fact that potency estimates developed by the Agency on the basis of information existing in the 1970's were used. In the 1970's, the practice of evaluating risk of cancer was dominated by concerns about chemical compounds directly altering DNA and genome. In the light of new discoveries, this practice is no longer adequate in the 1990's. New scientific data challenge previous concepts that all cancer-causing chemicals act solely through mechanisms recognized for radiation. New evidence has accumulated during the past ten years showing that chemicals produce cancer also by other mechanisms, e.g. through hormonal pathways, by mitogenic stimuli or by causing cellular death with compensatory cell proliferation. These advances in scientific knowledge have a major impact on the estimation of carcinogenic risk of chemicals (NAS/NRC, 1994).

Historically, the Agency formed its evaluation of carcinogenic hazards on principles recommended by U.S. HEW and U.S. FDA guidelines (U.S. HEW, 1969, U.S. FDA, 1971). These protocols determined what methods should be used for estimates of the carcinogenic risk and included a questionable recommendation that "testing should be done at doses and under experimental conditions likely to yield maximum tumor incidence". A log-probit one-hit model of carcinogenicity was used for mathematical extrapolation of evidence obtained in high-dose animal experiments to low doses effects (Mantel and Bryan, 1961, 1975).

When it was discovered that the low-dose region extrapolations by this procedure tended to zero much more rapidly than extrapolations assumed by somatic mutation models, the guidelines declared that the Mantel-Bryan procedure "lacks biological relevance" and is inappropriate for chemicals acting directly on DNA. Short-term laboratory procedures testing genetic alterations and neoplastic cell transformation in cells and tissue cultures were developed and the Mantel-Bryan approach was

replaced by a multistage model where no a priori assumption was made about the form of mathematical extrapolations. In order to assure that the procedures do not underestimate risk in some situations, the guidelines insisted that "linear extrapolation should always be included among any methods used" (U.S.IRLG, 1979).

Variable sensitivity to carcinogens due to genetic, racial and ethnic factors and other suspected modifiers was used to oppose the notion that "an observed no-effect level of exposure on animals or even in a specific human population will be applicable to the total human population at risk" (U.S.IRLG, 1979) and that "no reliable method is known for establishing threshold that could apply to the total human population"(IARC, 1977). These overprotective recommendations ignored the real mechanisms of action of chemicals and left a long-lasting imprint on many regulative decisions.

In 1984, the Office of Science and Technology Policy of the White House assembled a group of senior scientists to develop general principles for improving guidelines and assessing carcinogenic risks. The group emphasized gaps in understanding of the carcinogenesis process, characterized previous recommendations as "judgmental (science policy) decisions" and proposed that the guidelines be an "ongoing process that strives to periodically update current understanding of carcinogenesis and the scientific process of how this understanding is utilized" (U.S. OSTP, 1985).

First, new consensus reassured that "cancer can be induced by radiation, biological, physical and/or chemical agents" i.e. by a multifactorial pathogenesis than included mechanisms other than solely a chemical alteration of DNA. The experts accepted that cancer development is a multistage process that "may involve the genome, both indirectly (frequently termed epigenetic events) and directly, which may include the participation of chemicals or viruses".

Second, concerning animal testing for carcinogenesis the group carefully weighted existing presumptions (IARC, 1977) that "in the absence of adequate data in humans, it is reasonable for practical purposes, to regard chemicals for which there is sufficient evidence of carcinogenicity in animals as if they presented a carcinogenic risk in humans." The experts emphasized that this conclusion should not "foreclose further inquiry into the human relevance of animal carcinogens (U.S. OSTP, 1985).

The acceptance of an established "carcinogenicity in animals" has become a pivotal problem in further discussions of the risk assessment of human cancers. Different groups developed "decision rules" by which a chemical was declared a carcinogen (Weisburger, 1983). These attempts ranged from simple numerical approaches (two studies in two animal species - IARC, 1977) to a set of complex criteria that continued to develop with time (U.S. IRLG, 1979, Griesemer et al., 1980, IARC, 1980). Numerical differences in animal tumors at multiple sites and of unspecific origins were considered as evidence of chemical

carcinogenicity without questioning whether or not: (1) any observed tumors are more likely to have occurred by chance or as a result of treatment; (2) the observed lesions were directly related to the exposure; or (3) the use of the exposure route or maximum tolerated dose has been justified. The conservative approaches were accepted in spite of existing cautions against the use of doses so high that they produce "unwanted toxic side effects" (U.S.IRLG, 1979) or "unphysiologic conditions which may in themselves enhance tumor formation" (U.S. NCAB, 1977).

Modifications of these procedures have been used by the Environmental Protection Agency until the 1990's when the scientific community pointed out that chemicals that induce cancer at high doses in animal bioassay often lack traditional characterization of genotoxins. Non-genotoxic compounds have also a common property of increasing cell proliferation in the target organ that can account for the reported carcinogenicity (Cohen and Ellwein, 1990, Butterworth and Slaga, 1991). Moreover, Ames and Gold demonstrated that in chronic testing of chemicals at the maximum tolerated dose more than half of all tested compounds were carcinogens in animals although a high percentage of these chemicals showed no mutagenic effects. Because chronic dosing can be compared to a "chronic wounding", which is known to be a promoter of carcinogenesis in animals, it can be expected that most tested chemicals "are animal carcinogens when administered at chronic, near toxic doses" (Ames and Gold, 1990).

More than an adequate level of experimental evidence supports the proposal that the testing of chemical carcinogens should be changed. Thyroid follicular cell tumors produced by chemical substances were interpreted as products of long-term hormonal disturbances caused by chronic toxicity and not by chemicals interacting with genome (U.S. EPA 1988). Male rat kidney tumors after exposures to high concentrations of gasoline vapor were explained by the toxic action on renal tubular cells with resulting cell proliferation and tumors due to accumulation of a protein that is specific to male rats but not found in humans (U.S. EPA, 1991). Many other substances including natural products such as d-limonene cause kidney tumors in male rats but do not similarly affect other rodents or humans.

Long-term exposures to Diesel exhaust have shown that high particle loads block lung clearance, lead to an excessive accumulation of particulate matter in the lung and result in formation of lung tumors (Mauderly et al., 1986, Stoeber, 1986, Brightwell et al., 1986). However, the tumor action is independent of the presence of chemical carcinogens and occurs whenever inert materials accumulate in the lung. The tumors appear due to physical rather than chemical properties of the tested material and are independent of the presence of carcinogenic chemicals in the extractable soot (Vostal, 1986, 1994, Nikula et al., 1991, Mauderly et al., 1991, Heinrich and Fuhst, 1992).

Other studies demonstrated that carcinogenicity of formaldehyde displays a nonlinear dose response curve where the tumor incidence

decreases more rapidly than dose and indicates a no-effect level (Casanova et al., 1992, Cotruvo et al., 1992). New "biologically based" approaches concluded that before dioxin can cause any of its harmful effects, including cancer, the chemical must bind to and activate an aryl hydrocarbon receptor. Only after a certain number of cell receptors has been occupied, the biological response and cancer can occur (Roberts, 1990). Again, this shows that a "threshold" or no-effect level exists for receptor-binding substances below which no toxic effects occur.

Non-genotoxic mechanisms may be also responsible for formation of tumors in chemicals where exact mechanisms have not yet been evaluated. For example, new evidence on benzene suggests that similarly as leukemia is produced by bone-marrow depleting drugs, benzene-induced occupational cancer (leukemia) may be a secondary effect of bone marrow toxicity with reactive cell proliferation. Reassessment of data indicates that occupational exposures to benzene were underestimated (Paustenbach et al., 1992) and thus, did not exclude the possibility of hematopoetic toxicity prior to the secondary carcinogenesis.

These discoveries indicate that the EPA's default model of linear multistage extrapolation has no universal validity and needs to be replaced with more realistic approaches once mechanisms are better understood.

(B) Alternative Approaches

The evidence challenging traditional interpretation of animal data seriously questions continuing use of carcinogenic potencies developed under "default principles" in late 1980's. In fact, their use can prevent a more effective management of environmental risks or important regulatory decisions.

The nonlinearity of the dose response curve and potential existence of a no-effect level is at issue because genotoxic chemicals are not expected to exhibit a threshold at low concentrations. However at high doses, the toxicity of genotoxic compounds may cause cell death and result in tissue proliferation in addition to the genotoxic action. The final result is, therefore, either a genotoxic effect, a proliferative effect or both, independent of whether or not the process affects normal or initiated cells.

In contrast, non-genotoxic chemicals can be categorized by their mechanism of action. Some interact with cellular receptors, other act through non-receptor mechanisms such as cytotoxicity, mitogenic stimuli or by causing a hormonal imbalance. Most if not all cytotoxic compounds are expected to have a no-effect threshold above which cytotoxicity becomes apparent. Below this threshold, cytotoxicity is not manifested and increased cell proliferation with cancer-producing effects would not occur. Any interpretation of long-term bioassays as well as the risk assessment process "must take into account these aspects of non-

genotoxic mechanisms before linear multistage models are automatically used in risk calculations" (Cohen and Ellwein, 1990).

Based on these discoveries, scientific community insisted "that the existence of an observable threshold in carcinogenicity be recognized and that environmental policies and regulatory guidelines should follow these new discoveries" (Ames and Gold, 1990). Important precedents for the policy change have already existed and threshold-assuming models have been proposed in cases of documented evidence of hormonal imbalance or cytotoxicity (U.S. EPA, 1988, 1991).

The U.S. EPA became concerned about "the institualization of the default cancer risk assessment methodology" issue and in 1989 assembled experts to examine scientific foundations of the 1986 Carcinogen Risk Assessment guidelines as the first step in the Agency's review of the risk assessment methodology (U.S. EPA, 1989). A Risk Assessment Forum was established to promote scientific consensus on risk assessment issues and to ensure that this consensus is incorporated into appropriate risk assessment guidance. In addition, a Working Group on Risk Assessment Practices in the federal government was formed to examine opportunities for collaboration on methods and research among agencies engaged in risk assessment. An intergovernmental public meeting on risk assessment methodology was convened in Washington, DC. to focus on improvement of specific risk assessment issues (U.S. DHHS, 1991). A survey indicated that some principles identified in the 1985 OSTP document need to be changed. Principles discussing the mechanism of cancer induction, the role of cell proliferation and receptor-mediated carcinogenesis, as well as principles discussing the existence of a threshold, use of maximum tolerated doses and low dose extrapolation models were the primary candidates to be reviewed (Hart, 1991).

The most recent effort to address public skepticism about the reliability of scientific predictions concerning possible threats to human health comes from the National Academy of Sciences/National Research Council Committee on Risk Assessment of Hazardous Air Pollutants that concluded that "as scientific knowledge increases, the judgmental (science policy) choices made by the Agency and Congress should have less impact on regulatory decision-making. Better data and increased understanding of biological mechanisms should enable application of risk assessments that are less dependent on conservative default assumptions and more accurate as predictions of human risk" (NAS/NRC, 1994).

To reduce the uncertainty and increase the scientific validity of the decision-making process, the NAS report recommended that iterative, estimate-improving assessments be rigorously "conducted until:

(1) the risk is below the applicable decision-making level;
(2) further improvements in the scientific knowledge would not significantly change the risk estimate, or
(3) the Environmental Protection Agency, the emission source or the public determines that the stakes are not high

enough to warrant further analysis" (NAS/NRC, 1994).

Instead of a single estimate produced by the default output, the risk assessment should become "a process for summarizing the available scientific information in both qualitative and quantitative form". The application of generic guidelines with the intention to avoid underestimating health risk ("plausible default conservatism") is not objected to in general but the scientific community believes that "its use should not be allowed as a criterion in deciding when science can be used to replace a default option. As new scientific information is developed and used to replace default options, the result will typically be a reduction both in the estimates of risk and the extent of uncertainty in the risk assessment" (McClellan and North, 1994).

Iterative approaches advocated by the NAS report offer a plausible solution how risk estimates can be improved so that the decision-making process can be based on a sound scientific knowledge. The approaches can be organized in the form of one or more probability distributions and by summary statistics computed through Monte Carlo analysis or other probabilistic analysis techniques. By knowing the central tendency estimates and statistical confidence limits, the decision makers and the public will better understand the implications of probability distributions (NAS/NRC, 1994). The Motor Vehicle-Related Air Toxics analysis would benefit from accepting this iterative approach because it will not only improve the scientific accuracy of its estimates but will also indicate the level of uncertainty by more descriptive zero-to-upper-bound ranges.

On the other hand, approaches recommended by the NAS report do not offer an automatic solution for the non-linearity of the dose response curve and the no-effect level (threshold) applications. However, the Risk Assessment Forum has already on record a significant, threshold-assuming precedent in the form of its 1991 document concerning male rat kidney tumors. The document declared that secondary toxicity-induced and threshold-displaying neoplasms are not relevant to the risk assessment process and that "such tumors are not included in dose-response extrapolations for the estimation of human carcinogenic risks" (U.S. EPA, 1991). Even if this conclusion fails to provide a specific directive how the non-linearity of the dose response curve should be treated or how the no-effect level for carcinogenicity should be established for other chemicals, returning to the threshold-assuming extrapolation procedures might be one of many solutions proposed by the NAS report.

The NAS review insists that "scientific information, to the extent it is available, should be used as much as feasible in the risk assessment process" but that "guidelines are necessary to structure the interpretation and use of scientific information and to guide actions when information is incomplete or absent in particular assessment" (McClellan and North, 1994). It is encouraging that the new draft of U.S. Environmental Protection Agency guidelines (now in the final review process) has already recognized the role of cell proliferation,

the non-linearity of the dose response and the existence of a population response threshold (U.S. EPA 1994). The document introduces both linear and nonlinear extrapolation procedures for use in specific cases and promises that the new risk assessment procedures will be based on a more solid science than ever before. The new guidelines should be available in the near future and it would be advisable that the promulgation of air toxics regulations be delayed until the assessment can be upgraded under the new directives.

(C) Uncertainties

Table 1 illustrates changes in the carcinogenic potency of chemicals as new scientific data have been developed and used

Table 1. Comparison of the U.S.EPA-Published Unit Risk Factors (data from U.S. EPA documents)

Pollutant	May 1985	June 1988	% Change
Benzene	6.9×10^{-5}	8.3×10^{-6}	- 88
1,3-Butadiene	4.6×10^{-7}	2.8×10^{-4}	+ 60770
Formaldehyde	6.1×10^{-6}	1.3×10^{-5}	+ 113
Gasoline Vapor	7.5×10^{-7}	6.6×10^{-7}	- 12

between 1985 and 1988. Developments in testing methods and cancer understanding resulted in differences between EPA-derived unit risks of 1,3-butadiene that exceeded three orders of magnitude just in a period of three years. Similar dramatic changes for 1,3-butadiene or other chemicals can be expected in the future.

If this instability of unit risks indicates a high level of uncertainty in evaluating the carcinogenic potencies, any study that uses these estimates should indicate a corresponding potential for error also in its final estimates. The sole fact that the potency estimates have been changing with the progress of science suggests that even the potency for 1,3-butadiene may be significantly reduced by future discoveries and thus influence the study results.

EPA's new guidelines recognize that "not every EPA assessment has the same scope or depth" and that the "picture will change as research reveals more about carcinogenic process". When adopted by the Agency, the "guidelines will apply prospectively to new assessments and to revisions of previous assessments prompted by new data that may alter

previous conclusions" (U.S. EPA, 1994).

This instability of the unit risks on record indicates a strong possibility that the inherent uncertainties in the carcinogenic potencies might have significantly influenced the accuracy of the Air Toxics study predictions.

E. Impact on the Study

It can be expected that introducing new science into the Motor Vehicle-Related Air Toxics study would have a strong impact on the outcome of the assessment because the application of threshold-displaying models may reduce risk estimates for Diesel, formaldehyde, acetaldehyde or gasoline vapors to levels not statistically different from zero. The same mechanisms may potentially apply also for benzene. This leaves 1,3 butadiene as the only measurable risk of the health risks of air toxics from mobile sources.

Additional risk reductions can be introduced by the fact that under the direction of the Clean Air Act, declines in motor vehicle-related hydrocarbon emissions have already occurred and will continue in the future (U.S. EPA, 1993b). For example, the emission rates for an average vehicle on the road will be about 90% lower in the year 2010 than in 1988. Further emission gains will be achieved through modification of fuels that will occur under the requirements for reformulated gasoline, especially for benzene. As the combination of fuel and vehicle controls reduces volatile organic compound, the air toxics emissions will be equally lowered and proportional reductions can be expected in public risks (Leonard, 1992).

(D) Communication

The report is well written and uses understandable language making the information easily available for risk managers and for interested members of the public, including lay community. The report's summary should, however, emphasize the magnitude of uncertainties and the numerical results should be presented in the form of frequency distributions or iterative computer runs rather than by the point values. Wherever possible, the sensitivity analyses should be conducted on the variability and distribution of different ambient concentrations or exposure estimates and the final results should be presented as ranges starting from zero up to the upper bounds. Only then will the reader receive satisfactory information about the statistical robustness of proposed predictions and potential risks.

CONCLUSIONS

Automotive emissions have been the center of national attention in improving the air quality for two decades. As a result, concerted efforts of the regulatory process and innovative control technologies

substantially improved the air quality nationwide (U.S. EPA, 1993b). The magnitude of this improvement is unprecedented in comparison with any other pollution prevention process in worldwide history.

Legislative mandates requesting evaluation of the residual risks for human health from unregulated emissions in 1990's represent, therefore, a frustrating task for detecting effects that should have been explicitly manifested long before controls of automotive emissions have been introduced.

In spite of these difficulties, the Office of Mobile Sources prepared an excellent engineering analysis of the first step in the identification of risk - an estimate of the level of exposure. However, this excellent exposure analysis has not been matched by equally improved assessment of the studied biological endpoints. The efforts of the authors were seriously limited by the uncertainty of potency estimates that were based on information obtained in 1970's. The validity of these assessments is questioned in light of new discoveries and scientific advances that occurred in 1990's.

The scientific community agrees that cancer prevention is important but requests that more information should be obtained on carcinogenic mechanisms of airborne pollutants before unjustified approaches are used in assessing their risks and premature conclusions are presented as a basis for regulatory needs.

It has been repeatedly argued that the low human exposure to many air toxics poses little or no risk of cancer because high doses used in rodent bioassay cause tumors by inducing cytotoxicity with resultant cell proliferation rather than by directly initiating DNA damage and mutations. If mitogenetic mechanisms prevail in the carcinogenic process and a threshold exists for these epigenetic actions, the used "default" risk assessment process with linear low-dose extrapolation for all chemical carcinogens regardless of mechanisms of action, is unjustified and may result in a serious overstatement of risks that do not exist.

The provisions of the Clean Air Act mandate that "the Administrator of EPA shall enter into appropriate arrangements with the National Academy of Sciences to conduct a review of .. .. risk assessment methodology used by the Environmental Protection Agency to determine the carcinogenic risk associated with exposure to hazardous air pollutant" (CAA, 1990). Similarly, the scientific community calls for modification of the outdated "dependence of EPA's policy on studies involving administration of huge levels of chemicals to rodents and highly conservative modes of extrapolations to low doses in humans with the further assumption that at trivial doses a carcinogenic effect exists" (NAS/NRC, 1994).

The NAS review has been completed and the Agency's Risk Assessment Forum is finishing the long-expected update of the carcinogenesis guidelines (draft in review process). These guidelines dramatically

change the existing EPA's views on carcinogenesis and methods how it should be evaluated. It may be expected that estimates conducted under the new guidelines will significantly reduce the public health risks from air toxics from mobile sources and may demonstrate that these risks are so small that they cannot be differentiated from other everyday life risks. The necessity of upgrading the assessment process on the basis of more current science and EPA's new carcinogenicity guidelines should be seriously considered before the results are used in risk management decisions and the final rulemaking process. Otherwise, unnecessary regulations will impose cost on society that would not convey corresponding benefits in terms of health protection.

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Review of "Motor Vehicle-Related Air Toxics Study"
Prepared for the U.S. EPA

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Task 1) Adequacy and appropriateness of using the HAPEM-MS model to estimate annual average exposure to motor vehicle-related air toxics.

The HAPEM-MS model was originally developed to describe carbon monoxide exposures from mobile sources. It was based on the ambient air concentration measurements of CO in rural and urban areas, population activity pattern of residents in Cincinnati to determine the time spent in different microenvironments, population census for rural and urban settings and field studies conducted in Denver to relate the ambient concentration measurements to predicted concentrations in the microenvironments. The model uses the assumption that only five microenvironments are necessary to estimate CO exposures from mobile sources. These include two highly impacted by automobiles: inside a motor vehicle and outdoors near roadways. The output from the MOBILE4 or MOBILE5 is used to provide emission factors for particular regions and years to the model for different car fleets and new model years, so that an update of the emission distribution of CO from automobiles as well as predicting how proposed changes affect the distribution. The model has been altered to allow for the prediction of exposure to other air toxics from mobile sources by assuming there is a constant ratio of CO concentration to air toxic concentrations in the emissions and all microenvironments.

The original concepts for CO prediction are reasonably well founded, though there are some limitations because of the limited data bases available for use, as was mentioned in the report. The report also states that there are uncertainties "regarding the use of CO as a surrogate ... (because) (t)he microenvironmental factors may vary by pollutant." The use of the HAPEM-MS model for air toxics is dependent upon the extrapolation of CO data and microenvironmental factors to other air toxics. This represents a potential basic flaw which needs to be validated prior to using this model to estimate air toxics exposures. The validation attempted in this report, comparing the HAPEM-MS model prediction of the ambient air concentration range with a corrected measured ambient air concentration range attributed to automobile emission, does not adequately test the model's ability to estimate total exposure and agreement between these ranges should not be considered an indication that the model is able to predict the exposures associated with all microenvironments.

The following are some of the limitations of the HAPEM-MS model as it was used in this report. Each assumption used (some of which are mentioned in this report) needs verification prior to having confidence in the results.

One limitation is the extrapolation of ambient CO measurements to microenvironmental CO measurements nationwide from a single study done in Denver during four months of the winter. Denver is at an elevation of 1200 m, which results in different emission profiles for automobiles compared to those at sea level, where the majority of the U.S. population lives. These microenvironmental factors need to be validated in other regions of the country and other seasons. This is particularly true for rural areas where concentrations within an automobile are highly related to proximity to other automobiles, which would not be reflected in the ambient air monitoring station data. The use of extrapolation from central sites can be expected to better estimate means than the extremes in the distributions, since relative proximity to a source, which varies between the microenvironments and the ambient monitoring stations, affects the extremes of the distribution more than the mean. Thus more caution is needed when attempting to use the HAPEM-MS model for estimating the 95th percentile exposed population, particularly using a single scaling factor.

A second limitation in the appropriateness of using the HAPEM-MS model is extrapolating the Cincinnati time activity pattern data to the US as a whole, even after adjusting for the seasonal differences that exist in different regions of the US, as was done in the model. Differences in lifestyles and culture can also result in different activity patterns, including how and when automobiles are used. It is important to address this when attempting to utilize the model on a national scale. Data currently exist in California for comparison and national time activity pattern studies are currently underway sponsored by EPA and EPRI under the direction of John Robinson.

A third limitation to be addressed is the number of microenvironments that should be included. Five

were chosen for the model, but other microenvironments impacted by mobile source emissions, such as public and private parking garages, may contribute measurably to the exposure even though they may only be occupied for a small amount of time.

The largest limitation in applying the HAPEM-MS model to air toxics, as mentioned above and indicated in the report, is the extrapolation of data collected for CO to air toxics by assuming a simple ratio. This is problematic for two reasons. The first is CO is purely an exhaust emission, while some of the air toxics have contributions from both exhaust and evaporative emissions. Thus the HAPEM-MS model will underpredict any situation where evaporative emissions become important. The second is differences in the atmospheric reactivity of CO and some air toxics. This will result in altering the ratio between the source emissions, various microenvironments and ambient monitoring sites, which are used to estimate the microenvironmental exposures.

The ratio of the compounds emitted in the exhaust can also vary with fuel content, automobile conditions and control devices. While the variance with fuel is addressed through the use of the MOBILE5 model, data are needed to validate these ratios for different parts of the country using in-fleet vehicles and alternate fuels.

Contributions by evaporative emissions in specific microenvironments, such as parking garages and service stations, can be the dominant sources of air toxics and can contribute measurably to the daily exposure of air toxics originating from mobile sources. CO does not have an evaporative component, thus no contribution to its daily exposure via evaporation is observed, or included in the HAPEM-MS model. In addition, even in microenvironments where exhaust emissions are often more important than evaporative emissions, under some conditions evaporative emissions can become important, for example in the interior of automobiles evaporative emissions from the engine of the car being driven can penetrate the cabin adding to the exposure of air toxics with no corresponding CO additions. These types of emissions contribute to the overall exposure because of the proximity to the source, and would not be reflected at an ambient monitoring station.

2) Adequacy of the source apportionment estimates

An emissions inventory apportionment was used to derive the portion of the measured ambient air concentration associated with mobile sources. This approach has a fairly large uncertainty since emission inventories are often inaccurate, can represent maximum permitted not actual releases, do not provide information on temporal changes in the emissions which are important since most ambient data sets used were for a limited time period, do not take into account the spacial distribution of the point source emissions relative to the monitoring site (except when specific sites were being eliminated because of proximity to large non-mobile sources) and variability among cities could exist. However, the apportionment was only used as an adjustment of the atmospheric concentration for comparison to the HAPEM-MS model predictions, which probably has a greater uncertainty inherent in it. If the apportionment estimate is to be used to directly estimate exposure then validation of the emission inventories for each site examined is required or more sophisticated methods based on the composition of the air samples should be attempted.

3) Definition of the contribution of atmospheric transformation products to motor vehicle related air toxics exposure.

The report indicates that atmospheric transformation of formaldehyde, 1,3 butadiene, acetaldehyde and diesel particulate matter occurs between the source emissions and the ambient air monitoring stations while it assumes that benzene is stable. These assumptions appear to be valid, though a complete knowledge of the transformation chemistry of diesel particulate matter is not known. However, the applicability of only looking at the transformations as they apply to the ambient site and attempting to extrapolate the ambient air concentrations to microenvironmental concentrations, is not appropriate for evaluating exposure. The concentration within each of the microenvironments (i.e. indoor, automobile cabin) need to consider both the appropriate light and dark reactions that occur during transport and in microenvironments and not just in the ambient air. The concentrations of air toxics and/or their precursors change from their point of emissions and these changes must be considered where and when the actual

exposure occurs when attempting an exposure model.

4) Evaluation of the comparison of the HAPEM-MS exposure to ambient monitoring data and the reasonableness of the final exposure estimates resulting from the adjustment of HAPEM-MS exposure to match the upper end of the ambient data.

The applicability of each air toxic will be discussed separately. Overall there are too many limitations in applying the HAPEM-MS model nationally to air toxics (other than CO) to have a large degree of confidence in the resulting mean exposure values, and even less confidence in the 95th percentile value. A major field study to validate the exposure in all microenvironments is needed for each air toxic to assure the applicability of an HAPEM-MS type model. The report indicates for several compounds that the exposure estimates have uncertainty and that warning should be heeded pending a field evaluation of the air toxics exposure across all microenvironments.

The adjustments of the HAPEM-MS exposures to match the upper end of the ambient data have a number of qualifiers as discussed in #1 and #2 (above). Further, while general agreement was found between the HAPEM-MS predicted mobile source contribution to the ambient air and the adjusted ambient air data, this comparison is not deemed to be a satisfactory check on the HAPEM-MS model's ability to predict total exposure because much greater differences are expected in the exposures in microenvironments between CO and the air toxics than are expected in the concentrations at ambient air monitoring sites distant from the source emissions. The two correction factors used, one to adjust ambient air concentrations to microenvironmental/activity patterns and the second to give a mobile source contribution, also may have large uncertainties associated with them and a number of broad assumptions were made when deriving the value, so only limited confidence should be placed in them.

Application to benzene: The ambient air concentration measurements are considered to be reliable for benzene and for urban areas an extensive data set is available, but the portion attributable to mobile sources is less certain for each site. A potential problem with the use of the ambient monitoring sites is they were not selected to be used to estimate population based exposures, as is being attempted here, but were selected to examine locations which were likely to be impacted by VOCs, though not necessarily from mobile sources. This could result in either an overestimation of the benzene mobile source contribution, by having larger than usual industrial benzene sources in an area or avoiding areas with traffic within a region, or an underestimation, by having the sampling site closer to heavily trafficked areas than desired for a population based study. The sampling locations should be examined to assure their appropriateness.

The estimate for the 95% has a higher degree of uncertainty than the mean since exposures to the air toxics from mobile emissions would be occurring near the source, such as when driving a vehicle, and this may not be adequately modeled by CO measurements in the microenvironments. Further the extrapolation from ambient sites distant from the source tends to underpredict concentrations in the 95th percentile.

A greater concern, which was addressed in detail in #1 above, is the use of the microenvironmental factors derived for CO for benzene, which has evaporative emissions, and will result in an underestimation of the potential total exposures to mobile source emissions.

Applications to formaldehyde: The ambient data for formaldehyde is extensive, though the same caveats about using the data base for population based estimates indicated for benzene apply for formaldehyde as well. As noted in the report, there is some question as to whether high ambient ozone levels may have resulted in the measured formaldehyde concentrations being less than the true concentration. The attempt to apply the HAPEM-MS model to estimate formaldehyde exposure based on the ambient air concentration is fraught with difficulty, as is stated in the last paragraph of section 6.5.2 "Any formaldehyde exposures projected by HAPEM-MS itself should be viewed with caution". This arises from not only the reactivity differences between CO and formaldehyde in the atmosphere and the attempt to partition the percent of primary and secondary formaldehyde at the monitoring station, but also because the percent of primary and secondary formaldehyde will vary in the different microenvironments. The microenvironmental exposures are further confounded by the distance from the sources (in-vehicle

exposures may be dominated by primary mobile source emitted formaldehyde while indoor air exposures may be dominated by secondary sources), and time of day.

Application to 1,3 butadiene: As was indicated in the report extrapolation of the HAPEM-MS model to 1,3 butadiene is problematic because of greater reactivity than CO, which for the summer results in residence times of < 1 hour. This would result in a questionable ability to predict microenvironmental concentrations near a source from the ambient monitoring station data. Thus the factors developed in the HAPEM-MS model to describe the microenvironmental concentrations from the ambient air concentrations are not valid during the summer and the HAPEM-MS model should not be used to estimate exposure to 1,3 butadiene from mobile sources.

Application to acetaldehyde: The caveats provided in the report and listed above for formaldehyde apply to the use of the HAPEM-MS model for acetaldehyde.

Application to Diesel Particulate Matter: It is highly questionable as to whether the HAPEM-MS model, derived from CO measurements, a gas whose source is dominated by gasoline powered vehicles, can be extrapolated to diesel particulate matter, even though both are exhaust emissions which are non-reactive in the atmosphere. In addition to different sources (i.e. vehicle type), CO and diesel particulate matter have different removal mechanisms. No estimates of exposure for individual compounds are provided, presumably since insufficient data exists for making such an estimate. These estimates could be important for health risk calculations but will require a greater knowledge of the atmospheric transformation rates and microenvironmental concentrations than we currently have before attempting to calculate exposures.

6) Analysis of short-term microenvironmental exposures

The sections on short-term microenvironmental exposures indicate a number of microenvironments in which the daily exposure could be from minutes to a couple of hours. In several microenvironments evaporative emissions are important and other microenvironments are enclosed which results in a buildup of the emissions (as indicated in section 6.5.3). These issues are not adequately addressed in the current HAPEM-MS model, though recognized in the report. One of the microenvironments considered in the report is the service station. Data from occupation exposure related to refueling should be examined to determine their applicability to testing the exposure estimates. To better predict the exposures, field studies need to gather and models need to include information such as the types of emission controls at the service stations in the region (i.e. presence of Stage II controls), whether self-service or attendant assisted fueling of the automobiles occur and impact of spillage during fueling. Another factor that needs to be considered is evaporative emissions vary seasonally and regionally due to fluctuations in temperature and adjustments to the fuel composition done to decrease fuel volatility in the summer thereby minimizing releases of ozone precursors.

A statement is made in several sections of the report (for example 5-32, 7-20) that imply that short-term exposures are of concern only with non-cancer effects. While concern for non-cancer effects should be considered, the exposures within these microenvironments should be considered in calculating cancer risks as well, since these exposure can contribute a measurable percent of the total daily exposure. For example, the in-vehicle exposures occurs for an average of 1.8 hours per-day and can contribute 20% of the daily benzene exposure. An additional microenvironment mentioned is in an office building which would have an even greater duration and also must be considered in cancer risk estimates. These concerns are also applicable for 1,3 butadiene, since it has a high atmospheric reactivity, highest air concentrations are expected in microenvironments near exhaust emissions, which may be only a few hours a day. Further, even short exposures can be important in causing residual doses in the body, since short term exposures to VOCs can result in increases in body burdens for up to several hours (Raymer et al. 1991 J. Exposure Anal. and Environ. Epidem. 1,439-451; Weisel et al. 1992 J. Exposure Anal. and Environ. Epidem. 2 suppl. 1 55-69).

Additional concerns in dealing with microenvironmental exposure is that while the emission controls may reduce the emissions in newer, well maintained cars, the introduction of alternate fuels, particularly oxygenated fuels, may result in higher emissions of formaldehyde and acetaldehyde from older cars or

poorly maintained cars and therefore higher exposures in the enclosed microenvironments or close to the exhaust emissions. Thus exposure calculations should consider emissions that result from changes in fuels as they pertain to the current fleet and the "superemittors" when evaluating short term exposures.

7) Alternate approaches to estimating exposures

The most cost effective manner to estimate nationwide exposure to mobile source derived air toxics is to use a validated model that predicts the exposure. An HAPEM-MS type model is a valid approach, provided the data inputs are appropriate and validated for the intended extrapolations. The data inputs and validation need experimental data from both microenvironmental field studies (indirect exposure determination) and a total exposure field study (direct exposure determination) that measure the air toxics rather than uses a surrogate compound, such as CO, to estimate mobile source contributions to the air toxic concentrations. The indirect methods would be used to ascertain the concentrations in microenvironments over long time periods and in different sections of the country while the direct method would be a major field study to examine the total air toxic exposures, thereby assuring that the sum of the exposures in the microenvironments examined account for the total exposure that is received by the population. Evaluation of the high end of the exposure distribution in microenvironments most impacted by mobile source emissions are needed. These measurements should include automobiles that malfunction in a manner typical of the real-world. The inclusion of more accurate estimates of microenvironmental data are expected to produce higher exposure estimates than presented here and reduce the uncertainty of the estimate.

8) Exposure data needs for non-cancer health risks from the toxics emitted by motor vehicles and whether adequate data exist for each toxic.

If non-cancer health risks occur they will be in microenvironments of the highest exposure, either associated with super emitter vehicles/malfunctioning vehicles or affecting sensitive sub-populations. An additional potential for exposure that could result in non-cancer health risk is the introduction of alternate fuels that have been designed for use in new, well maintained cars but result in higher than predicted exposures when used in older cars. Since the maximum exposures are usually of concern for non-cancer end points, rather than an integrated average, the indirect exposure approach which measures microenvironmental exposure needs to be performed. These experiments should be done using a range of in-fleet vehicles which would encompass those with the highest potential emissions. The exposures should be examined under a variety of seasons and locations, since emissions will change, and it is difficult to predict what set of conditions results in the greatest exposures. For example: to estimate evaporative emissions the following parameters which affect emissions differently need to be considered: higher temperatures which result in more evaporation, the fuel volatility which is adjusted seasonally to decrease evaporation in the summer when higher temperatures occur, the differential between the fuel temperature and the gas tank temperature which can affect the vaporization, and coevaporation of the components which can increase the evaporation of less volatile species. Defining the sensitive population and their activities is also important to determine what exposures are of most concern for non-cancer endpoints, which are driven by acute exposures rather than chronic. These populations could include: multiple chemical sensitive individuals, pregnant women, children and individuals with respiratory ailments. The air toxics that are problematic for each group can vary and need to be considered individually. Chemically sensitive individuals and those with respiratory problems might have greater concern with lung irritants, such the aldehydes, while pregnant women would have more concern with alternate fuels that have teratogenic effects.

The maximum exposure for each of the air toxics listed in highly impacted microenvironments, which is needed for non-cancer endpoints, is generally lacking.

9) Other studies, analyses and information on exposure to mobile source emissions. These studies could be used to evaluate the validity of the assumption that CO can predict air toxic concentrations in microenvironments impacted by mobile sources. Since some of these microenvironments are affected by evaporative emissions it is suspected that the HAPEM-MS model would underpredict the exposure

compare to that being measured.

a) available at the time the study was complete

Bevan, Protor, Baker-Rogers and Warren, "Exposure to CO, respirable suspended particulates, and volatile organic compounds while commuting by bicycle" Environmental Science and Technology 25, , 1991. Provides measurement of exposures near roadways. Data can be used to evaluate that microenvironment which is part of current model. Since this microenvironment is dominated by exhaust emissions model results should match well for non-chemically transformed compounds. Due to the proximity to the source it is suspected that compounds that are destroy by atmospheric transformation will be underpredicted and those that are created overpredicted in this microenvironment.

Bond, Thompson, Ortman, Blanck and Sigsby "Self service station vehicle refueling exposure study" EPA/APCA Symposium on Measurement of Toxic Air Pollutants, 458-466, 1988. Provides measurement of air toxics that occur during self-service fueling of vehicles. Shows the effect of evaporative emissions on exposure and model is expected to underpredict those with evaporative source.

Braddock, Gamble and Lemmons "Factors influencing the composition and quantity of passenger car refueling emissions - Part I." SAE Technical Paper Series 861558. Inter. Fuels and Lubricant Meeting. PA, Oct, 1986. Provides a controlled study of the concentrations at different distances from the automobile gas tank during refueling operations. Shows the effect of evaporative emissions on exposure and model is expected to underpredict those with evaporative source.

Chan, Ozkaynak, Spengeler and Sheldon "Driver exposure to volatile organic compounds, CO, Ozone, and NO_2 under different driving conditions" Environmental Science & Technology 25, 964-965, 1991. Air toxic concentrations were measured within an automobile cabin in two cars driven along three routes in North Carolina (urban, highway and rural) during commuting times. Provides data for automobile cabin microenvironment for well maintained cars. Data can be used to evaluate that microenvironment which is part of current model. Since this microenvironment is dominated by exhaust emissions model results should match well for non-chemically transformed compounds. Due to the proximity to the source it is suspected that compounds that are destroy by atmospheric transformation will be underpredicted and those that are created overpredicted in this microenvironment.

Chan, Spengeler, Ozkaynak and Lefkopoulou "Commuter exposures to VOCs in Boston Massachusetts" J. of Air Waste Management Association 41, 1594-1600, 1991. Air toxic exposures were determined for commuters driving, walking and taking public transportation in Boston. Provides data for several microenvironments associated with commuting. Data can be used to evaluate those microenvironments, some of which are part of current model.

Fujita, Croes, Bennett, Lawson, Lurmann and Main "Comparison of emission inventory and ambient air concentrations ratios of CO, NMOG, and NO_x in California's South Coast Air Basin" J. of Air Waste Management Association 42, 264-276, 1992. An additional data base for evaluating the ambient air concentrations, expect to match model values well.

Weisel, Lawryk and Lioy "Exposure to emissions from gasoline within automobile cabins" J. of Exposure Analysis and Environmental Epidemiology, 2, 29-96, 1992. In vehicle concentrations were measured for VOC and CO while commuting in the NY-NJ metropolitan area. Provides data for automobile cabin microenvironment. Data can be used to evaluate that microenvironment which is part of current model. Since this microenvironment is dominated by exhaust emissions model results should match well for non-chemically transformed compounds.

b) Lawyrk, N. "Automobile commuter exposures to volatile organic compounds: Emissions, Malfunctions and Policy" Ph.D. Dissertation, Rutgers, The State University of New Jersey, 1994. A year long study that measured in-vehicle concentrations while driving during commuting time periods in the NY-NJ metropolitan area. Followed two set routes and used one newer and one older automobile. Provides seasonal data on exposures within the automobile cabin microenvironment. Data can be used to evaluate that microenvironment which is part of current model. Since this study includes automobiles that had evaporative emissions that affected the microenvironment during some time periods an underprediction of the air toxic exposure by the model is expected for non-chemically transformed compounds at those times.

c) U.S. EPA. The BEAM model, under the direction of J. Behar, EMSL, NV. This is a model to predict benzene exposures and includes a component related to automobile releases.

Cooperative agreement between U.S.EPA (EMSL, NV) and Edwin Furtaw, University of Nevada, microenvironmental exposure to mobile source emissions. This project measured residential garage exposure to benzene.

Cooperative agreement between U.S.EPA (AREAL, NC) and UMDNJ (Lioy and Weisel) microenvironmental exposure to gasoline and alternate fuels. This project is measuring benzene exposures in several microenvironments (residential garages, public parking garages and during refueling) and methanol exposure in residential garages when M85 fuel is being used.

Cooperative agreement between U.S.EPA (AREAL, NC) and John Robinson nationwide survey of human activity patterns. This project will provide a national data base for activity patterns that will include time spent in microenvironments related to automobile emissions.

Lioy, P.J. Weisel, C. P., Jo. W.K., Pellizzari, E. and Raymer, J.H. "Microenvironmental and personal measurements of methyl-tertiary butyl ether associated with automobile use activities", Journal of Exposure Analysis and Environmental Epidemiology, in press 1994. This paper describes exposure to a winter-time additive to gasoline (MTBE) that has high evaporative emissions.

Summary of Peer Reviews of Motor Vehicle-Related Air Toxics Study

1) Tadeusz E. Kliendienst

a) Recent research indicates that oxidation of hydrocarbons leads to formation of products (e.g., peroxyacetyl nitrate, PAN) that are substantially more mutagenic than precursors. Also, NO_x limited systems tend to be less mutagenic. The significance of these observations with respect to human health impacts is unknown.

b) In EPA's urban airshed modeling of benzene in St. Louis, there is a large discrepancy between modeled and measured values of benzene. Possible explanations for this discrepancy should be considered.

c) In EPA's urban airshed modeling of 1,3-butadiene in St. Louis, there is a rapid rise in 1,3-butadiene after 20:00 hours LST when NO_x levels are highest right after sunset, and 1,3-butadiene reacts relatively rapidly with NO_3. This apparent inconsistency should be addressed.

d) It is important to note that at the present time, ambient concentrations of toxic compounds cannot be accurately predicted based solely on emission rates, atmospheric dispersion, chemical removal and formation, etc. At the present time, experimental measurements of toxic compounds are the most reliable means of obtaining ambient concentrations and they must certainly be used to validate air quality models for toxic compounds.

2) Andrew Sivak

a) EPA should include three recent human studies relating benzene

exposure and leukemia in its benzene risk assessment.

b) Since there are non-linear dose-response data for benzene, it is unclear how the Agency can state that they support a theoretical linear low dose extrapolation.

c) EPA should have used the 1991 draft unit risk for formaldehyde, based on monkey and rat DPX data, in its calculations, rather than the 1987 unit risk.

d) EPA should have used newer and more rigorous NTP carcinogenicity data for 1,3-butadiene to calculate unit risk estimates used in the study.

e) EPA should have included more discussion of the mutagenicity of polycyclic aromatic hydrocarbons and nitrated polycyclics in the gaseous phase of diesel exhaust.

f) The use of a linearized model for the calculation of risk from particle exposure is simply wrong scientifically.

g) There appears to be no cause for a public health concern for cancer from exposure to motor vehicle exhaust, and it would seem that the agency could use its resources more productively on matters of higher concern.

h) The Agency should consider recent publications by Adam Finkel and others on communicating uncertainties in risk assessment calculations.

3) Thomas H. Stock

a) Although use of HAPEM-MS is a laudable first effort in assessing the health impact of exposure to air toxics from motor vehicles, it has many severe limitations which may render it inadequate for its intended use.

b) Although HAPEM-MS is a national exposure model, the microenvironmental exposure factors it uses to convert fixed-site concentrations to microenvironmental concentrations are based on data from only one city, Denver. Thus, there are many questions on how much these data can be used to generalize to other cities.

c) EPA developed an integrated exposure adjustment factor based on activity data from a California study. It is questionable how representative this is of the nation as a whole.

d) Given the limitations of the HAPEM-MS model, it is reasonable to "correct" modelled exposures to agree with adjusted ambient data, until a more realistic model is developed.

e) At this point in time, there are insufficient data on any air toxic to explore the relationships among ambient, microenvironmental, and personal exposure.

4) Jaroslav J. Vostal

a) Any new assessment of the potential public health risk of diesel particles should include recent data which indicate carcinogenicity of diesel exhaust is not associated with particle-bound organics.

b) Tumor responses to diesel particles are not linear at low ambient levels; thus, applicability of the linear dose-response model is restricted.

c) Since existing epidemiological data for diesel exhaust exposure does not include documented exposure, the use of epidemiological data in the risk assessment remains questionable.

d) EPA's default model of linear multistage extrapolation has no universal validity and needs to be replaced with more realistic approaches once mechanisms are better understood.

f) Reanalysis of study results should take into account EPA's new risk assessment guidelines.

g) The application of threshold-displaying models may reduce risk estimates for diesel particulate matter, formaldehyde, acetaldehyde or gasoline vapors to levels not statistically different from zero. The same mechanisms may potentially apply also for benzene. This leaves 1,3-butadiene as the only measurable risk of the health effects of air toxics from mobile sources.

h) The magnitude of uncertainties and numerical results should be presented in the form of frequency distributions or iterative computer runs rather than by point values. Also, sensitivity analyses should be conducted on the variability and distribution of different ambient concentrations or exposure estimates and the final results should be presented as ranges starting from zero up to the upper bounds.

5) Clifford P. Weisel

a) EPA's HAPEM-MS model is severely limited by extrapolating ambient CO measurements to microenvironmental CO measurements nationwide from a single study done in Denver during four months of the winter. These extrapolations need to be validated in other regions of the country in other seasons.

b) Time activity pattern data for areas other than just Cincinnati need to be included in the HAPEM-MS model.

c) The HAPEM-MS model included five microenvironments, but others, such as public and private parking garages, need to be included.

d) It is problematic to extrapolate air monitoring data collected for CO to air toxics because: (1) CO is purely an exhaust emission, while some air toxics such as benzene have contributions from both exhaust and evaporative emissions; (2)

atmospheric reactivity of CO and some air toxics is very different.

e) Exposures in microenvironments should be considered in calculating cancer risks, since these exposures can contribute a measurable percent of the total daily exposure.

f) The inclusion of more accurate estimates of microenvironmental exposure data are expected to produce higher exposure estimates than presented in the study and to reduce the uncertainty of the estimates.