Peer Review Workshop for EPA's Draft Toxicological Review of Halogenated Platinum Salts and Platinum Compounds Human Health Assessment

Reviewer Post-Meeting Comments

June 11, 2009

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(A) Oral reference dose (RfD) for halogenated platinum salts and platinum compounds **19**

(A1) An RfD was not derived due to lack of adequate data to characterize the health effects associated with oral exposure to halogenated platinum salts and platinum compounds. Are you aware of any data that might support development of an RfD for halogenated platinum salts and platinum compounds? 19

(B) Inhalation reference concentration (RfC) for halogenated platinum salts and platinum compounds **20**

(B1) The Merget el al. (2000) occupational epidemiological study was selected as the basis for the RfC. Please provide a detailed explanation of any strengths or weaknesses regarding the Merget et al. (2000) study that are not identified or adequately reviewed in the current assessment. Please comment on whether the selection of this study was the principal study is scientifically justified. Has the rationale for this selection been transparently and objectively described in the document? Please identify and provide the rationale for any other studies that should be selected as the principal study. 20

(B2) Pt-specific allergic sensitization, as measured by the development of a positive skin prick test (SPT), was selected as the critical effect for the RfC resulting from exposure to halogenated platinum salts. Please comment on whether the selection of this critical effect is scientifically justified. Is the rationale for this selection transparently and objectively described in the document? Please provide a detailed explanation. Please comment on EPA's rationale regarding adversity of the critical effect. Has it been objectively and transparently described and is it supported by the available data and your understanding of

the available scientific data. Please identify and provide the rationales for any other endpoints that should be considered in the selection of the critical effect. 22

(B3) The RfC was quantified for halogenated Pt salts from the Merget et al. (2000) occupational epidemiological study which provided exposure data from airborne soluble Pt measurements that were not further characterized for specific Pt compounds. Please comment on the scientific justification of the derivation of an RfC for halogenated Pt salts from measurements of airborne soluble Pt that were not further characterized for specific Pt compounds. Please identify and provide the rationale for any other approaches that should be considered in the derivation of an RfC for Pt compounds. 23

(B4) Is the statement that "The use of the RfC for Pt compounds other than halogenated Pt salts is not recommended as the similarity between these compounds and other soluble forms of Pt compounds is unknown" scientifically justified? Please identify and provide the rationale for any other characterization of the platinum compounds that are relevant to the recommended use of the RfC. 25

(B5) EPA has concluded that the allergenic activity of Pt is compound-dependent and sensitization effects appear to be restricted to the halogenated Pt salts. Please comment on whether this finding is justified and supported by the scientific evidence. 27

(B6) The Merget et al. (2000) study reported 13/115 workers in the high exposure group developed Pt-specific allergic sensitization (as determined by a positive SPT) during the 5-year study period. The Merget et al. (2000) study did not adjust its reporting of SPT positive individuals for smoking as a risk factor for developing Pt-specific allergic sensitization. Please provide comments on the potential impact of this approach and implications it may have for the RfC derived from this study. 28

(B7) The RfC was derived on the basis that chronic exposure at the dose level would not induce allergic sensitization. However, it is unknown if the RfC would be protective of exacerbation of symptoms in individuals previously sensitized to halogenated platinum salts. Please comment on whether the decision not to derive an RfC based upon elicitation of an allergic response as the critical effect is scientifically sound and has been transparently and objectively described in the document. 30

(B8) A NOAEL/LOAEL approach was applied to incidence data for Pt-specific allergic sensitization to derive the POD for the RfC. The available data are of marginal adequacy for BMD modeling because only three exposure groups (high, low, and no exposure) are available and only one of these groups has a non-zero response. However, BMD modeling was applied to incidence data for Pt-specific allergic sensitization for comparative purposes. Please provide comments with regard to whether the NOAEL approach is the best approach for determining the POD. Have the NOAEL approach and the BMD modeling approach been appropriately conducted and objectively and transparently described? Please identify and provide rationales for any alternative approaches (including BMR, model, etc.) for the determination of the POD and discuss whether such approaches are preferred to EPA's approach. 32

(B9) Insufficient information is available to predict potential variability in susceptibility among the general population to allergic sensitization from inhaled halogenated Pt salts. Please comment on the transparency, scientific rationale and justification for the use of an uncertainty factor of 10 to account for interindividual variability. Are the criteria and rationale for this selection transparently and objectively described in the document?

Please comment on whether the justification for selection of this uncertainty factor based on these data is scientifically justified and transparently described..... 34

(B10) A subchronic study (Merget et al., 2000) was selected as the principal study with allergic sensitization to halogenated Pt salts as the critical effect for the derivation of the RfC. Please comment on the transparency, scientific rationale and justification for the subchronic to chronic uncertainty factor of 10. Are the criteria and rationale for this selection transparently and objectively described in the document? 36

(B11) An uncertainty factor of 10 was used to account for deficiencies in the halogenated platinum salts and platinum compounds database. The inhalation database currently does not include a chronic, developmental, or a two-generation reproductive toxicity study. Overall, the basic toxicology of halogenated platinum salts and platinum compounds has not been well characterized. Please comment on the transparency, scientific rationale and justification for the selection of the database uncertainty factor. Please comment on whether the application of the database uncertainty factor adequately addresses the lack of toxicity data for halogenated platinum salts and platinum compounds. Are the criteria and rationale for this selection transparently and objectively described in the document? 38

(C) Carcinogenicity of halogenated platinum salts and platinum compounds 40

(C1) Under the EPA's 2005 *Guidelines for Carcinogen Risk Assessment* (www.epa.gov/iris/backgr-d.htm), the Agency concluded that there is *inadequate evidence to determine the carcinogenic potential* of halogenated platinum salts and platinum compounds. Please comment on the cancer weight of evidence characterization. Does the lack of available data support the conclusion that there is *inadequate evidence to determine the carcinogenic potential* of halogenated platinum salts and platinum compounds? Has this recommendation been transparently and objectively described in the document? 40

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Reviewer Biographies

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Raymond Biagini, Ph.D.
Senior Service Fellow
CDC/NIOSH
Biological and Health Assessment Branch

Dr. Biagini received his Ph.D. in Toxicology from the University of Cincinnati, College of Medicine in 1984 and has been Diplomate, American Board of Toxicology since 1985. Currently he is Senior Service Fellow at the National Institute of Occupational Safety and Health (NIOSH), Centers for Disease Control, in the Biological and Health Assessment Branch, after holding several previous positions with NIOSH since 1977. Dr. Biagini is a long-time member of the Society for Toxicology and the American Association of Immunologists. He has published peer reviewed research articles in such professional journals as the *Annals of Allergy, Asthma, and Immunology*, *Clinical and Experimental Allergy*, *Clinical and Diagnostic Laboratory Immunology*, the *Journal of Occupational and Environmental Hygiene*, and the *Journal of Occupational and Environmental Medicine* to name a few.

George Cherian, Ph.D.
Professor Emeritus
Department of Pathology
The University of Western Ontario

George Cherian is Professor Emeritus in the Departments of Pathology, and Pharmacology & Toxicology at the University of Western Ontario, London, Ontario, Canada. His research interests are in metal toxicology and cancer. Dr. Cherian is the author of more than 250 publications, book chapters and a book on metal toxicology. He has served in research grant review committees of MRC, Canada, NIH and US Army. He was co-chair of WHO/IPCS health criteria document task group for Zinc and a member of the task group for Cadmium

Rogene Henderson, Ph.D., DABT
Senior Scientist Emeritus
Lovelace Respiratory Research Institute

Dr. Rogene Henderson is a Senior Scientist Emeritus at the Lovelace Respiratory Research Institute. Dr. Henderson earned her Ph.D. in chemistry from the University of Texas in 1960 and her B.S./B.A. in chemistry/biology from Texas Christian University in 1955. She was a Fulbright Scholar in physical chemistry in 1955-1956 and held fellowships at the Universities of Texas and Arkansas.

Dr. Henderson's research interests are in three major areas: (1) biochemistry of the lung, particularly the surfactant lining layer — she has developed in vivo screening tests for pulmonary toxicants based on analysis of bronchoalveolar washings for biomarkers of lung injury and repair; (2) the mechanisms by which pulmonary inflammation leads to repair or to chronic disease (fibrosis, emphysema); and (3) the pharmacokinetics of inhaled xenobiotics (particularly vapors) and chemical-specific biomarkers of chemical exposure. She has recently conducted studies on the health effects of low-level sarin exposures in rats.

Dr. Henderson has been a member of: the U.S. Army Deployment Toxicology Science Working Group, a member and Vice-Chair of the Board of Scientific Councilors (BOSC) for the U.S. Environmental Protection Agency (EPA) Office of Research and Development; and a member of the American Cancer Society (ACS) Advisory Group on Cancer and the Environment. She is a former member of the NIEHS Advisory Council (1991-95), the Health Effects Institute Research Committee (1997-2005), and the National Research Council/National Academy of Sciences (NRC/NAS) Board on Environmental Studies and Toxicology (1998-2004). Dr. Henderson is a National Associate of the National Academy of Sciences.

Kenneth Rosenman, MD
Professor
Department of Medicine
Michigan State University

Kenneth Rosenman, MD, is a Professor of Medicine at Michigan State University. Dr. Rosenman is Board-Certified in Internal Medicine and Occupational/Environmental Medicine. He is a Fellow of the American College of Epidemiology and the American College of Preventive Medicine. Prior to going to Michigan State University in 1988, Dr. Rosenman was Director of Occupational and Environmental Health at the New Jersey Health Department and a faculty member in the Department of Epidemiology at the University of Massachusetts. He has an active research program in occupational and environmental disease with particular interest in pulmonary disease. He has published approximately 150 articles on occupational and environmental disease.

Andrew Salmon, Ph.D.
Senior Toxicologist and Chief
Air Toxicology and Risk Assessment Section
Office of Environmental Health Hazard Assessment
California Environmental Protection Agency

Dr. Salmon is a Senior Toxicologist and Chief of the Air Toxicology and Risk Assessment Section at the Office of Environmental Health Hazard Assessment, which is part of the State of California's Environmental Protection Agency (Cal/EPA). As a research toxicologist in industry and academia, Dr. Salmon has worked on cancer mechanisms, metabolism and pharmacokinetics, inhalation toxicology and safety evaluation for environmental and occupational exposures. His current activities include application of benchmark dose methodology and evaluation of special impacts on children's health in air toxics risk assessment. In addition to editing and contributing to numerous chemical-specific risk assessment documents and procedural guidance documents for the State of California, he is a contributing author on a number of papers published in journals such as *Preventive Medicine, Environmental Health Perspectives,* and the *Journal of Toxicology and Environmental Health*, and has made several presentations at meetings of the Society of Toxicology and Society for Risk Analysis. Dr. Salmon received his bachelor's and doctoral degrees in Biochemistry from Oxford University, U.K.

Reviewer Post-Meeting Comments: General Questions

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(G1) Is the Toxicological Review logical, clear and concise? Has EPA accurately, clearly and objectively represented and synthesized the scientific evidence for noncancer and cancer hazards?

Raymond Biagini	The toxicological review is logical, clear, concise and comprehensive and appears to have collated the scientific evidence for non-cancer and cancer hazards.
George Cherian	The draft toxicological document of platinum compounds reviews several studies published in this field. The draft review is logical and concise but certain studies have been repeated in several sections. There are only few studies on the toxicity and carcinogenicity of platinum compounds in experimental animals. The subchronic oral exposure study of platinum compounds has several limitations in experimental design and end points, and do not allow identification of health hazards. The inhalation studies also have similar limitations on design but suggest allergic sensitization as a toxic effect. The data from these studies cannot be used for dose response analysis or calculation of The No-Observed Adverse Effect Level (NOAEL) or reference concentration (RfC). However, these limited toxicological studies suggest that halogenated platinum salts have higher toxicity than nonionic platinum compounds. A few of the occupational and epidemiological studies in platinum refinery and catalyst production plants report health and toxic effects such as respiratory irritation and allergic sensitization in humans repeatedly exposed to platinum compounds by inhalation. Most of these case reports describe health effects associated with inhalation of halogenated platinum compounds. The insoluble platinum compounds are considered inert. Three epidemiological studies on occupational exposure have reported exposure data that permit limited quantitative estimation of the average air platinum levels at work place and measure the response to skin prick test (SPT) in workers. The authors of the review have used exposure data from a prospective cohort study among German catalyst production workers ((Merget el al 2000) and were considered for bench mark dose (BMD) modeling for further analysis. The development of platinum specific allergic sensitization in workers was measured by the incidence of a positive SPT to hexachloroplantic acid, after exposure to halogenated platinum salts. In the five year study, air soluble platinum concentrations were measured in three groups of workers (high exposure, low exposure and no exposure) only two times but showing a large degree of variation. Moreover, there are few other limitations to the data collected in this study, including lack of speciation of platinum compounds. The calculations are made for exposure to halogenated platinum salts but there may be variations in halogen atoms in these compounds. Therefore, the confidence level of the key selected study is low, and thus the low confidence level of calculated NOAEL and RfC values in the draft review. There are no animal studies on chronic effects of platinum compounds. Few of the subchronic studies suggest that most of the platinum is accumulated in the kidney after oral and inhalation exposure, and kidney may be considered as a critical organ. Treatment of cancer patients with cisplatin also showed toxicity to kidney. There are no life time exposure studies to conclude the carcinogenicity potential of platinum compounds. Animal studies show that cisplatin can be a carcinogen and is classified as Group 2 B by International Agency for Research on Cancer (IARC). Cisplatin is also a mutagen in *in vitro* assay. Summary after each section in the document is useful.
Rogene Henderson	The review was thorough, well-organized and clear. I especially liked the summary paragraphs at the end of each section. I appreciated Table 2-1 and how it showed the

structures and properties of the various Pt compounds.

I would have liked a separate section summarizing potential human exposures in the environment, as opposed to occupational exposures. A partial discussion of this comes at the end of the introduction, but I think it should be expanded and have a separate chapter listed in the index for ready access. It would have been helpful to have a summary of how the general public are exposed to platinum compounds in air and in water and to what amounts and to what forms. Since the RfC is based on occupational exposures to soluble halogenated platinum salts, it is important to know the extent to which the public might be exposed to these forms of platinum.

In the chapter on chemical and physical information, it. would be helpful to discuss the limits of detection for the analytical procedures used to assay for platinum compounds. This is particularly important for an RfC of one pg/m3. How large a sample volume taken for how long a time would be required to detect this level of platinum. Another topic that should be covered is the stability of the different platinum compounds in the environment. If platinum is emitted from catalytic devices in cars in insoluble, oxidized forms, can these forms be converted to soluble forms? I doubt that they are, but the chemical information needed to evaluate this possibility should be given.

I would like to see a summary table of regulated levels from other agencies. For example the occupational TLV recommended by the ACGIH is 2 ug/m3. The WHO ICPS, 1991 states that this is the occupational value in most countries. Are there environmental levels from other countries?

Kenneth Rosenman

Overall the toxicological review is well written and a logical summation of the scientific evidence. Some points that could be made clearer:

1) That the RFC is for halogenated platinum salts and not other platinum compounds,

2) Fate of different platinum compounds that are released into the environment, i.e. more information on the chemistry/transformation of different platinum compounds in water, air and soil.

3) Environmental distribution of different platinum compounds to justify the need for developing an RFC

Major points made in response to specific questions:

Since cis-platinum has evidence of carcinogenicity and is a platinum compound, the summary statement in section 6.2.3 on pg. 164 doesn't adequately represent data. The reason for not discussing possible modes of carcinogenic action (4.7.3, pg. 131) is not adequate.

Review of the epidemiologic studies needs to systematically consider two other limitations: exclusion of workers at increased risk because of exclusion based on a pre-placement exam; and the loss of symptomatic workers from the study cohort.

Some of the clinical descriptions need to be rewritten to reflect more up to date and customary medical nomenclature.

I have concerns about two of the uncertainty factors used, one for chronic effects and the one for data base uncertainty. Changing these two factors would change the final

	determined RFC. None of my other comments would change the proposed RFC.
Andrew Salmon	The Review is for the most part clear and well-written, and presents a thorough review of the available evidence on the non-cancer toxicity of platinum compounds of concern as potential environmental contaminants. The presentation of evidence on cancer hazards is much briefer, due to the lack of clear evidence for or against carcinogenicity of platinum compounds other than for the platinum-based anti-cancer drugs (cisplatin *etc*.). The conclusion presented, that the evidence is insufficient to reach a conclusion as to potential carcinogenicity of the halogenated platinum salts and other inorganic platinum compounds, is undoubtedly correct – indeed, inevitable – but there may be room for some further consideration and review of the differences in structure and reactivity between cisplatin (a known carcinogen) and similar drugs, and the halogenated platinum salts.

(G2) Please identify any additional studies that should be considered in the assessment of the noncancer and cancer health effects of halogenated platinum salts and platinum compounds.

Raymond Biagini	Dermal exposure studies looking at a pulmonary endpoint may be called for. As pointed out in the review "Available data from occupational studies do not allow the determination of the relevance of dermal exposure in the development of allergic sensitization to halogenated Pt salts." There is evidence (Murdoch and Pepys [1986] and unpublished information) that the Pt salts can act as adjuvants in their own right, enhancing the allergic response to other allergens. Studies should be designed to further investigate this possibility.
George Cherian	I am not aware of any other published studies that can be considered in the assessment of noncancer and cancer health effects of halogenated platinum salts and other platinum compounds.
Rogene Henderson	I know of no additional studies that should be included.
Kenneth Rosenman	Two references (Friedman-Jimenez 2000 and Barnes 1989) should be replaced with more up to date citations. Friedman Jimenez 2002 → Ortega et al AJIM 2002,42:50-54 and Chester et al AJIM 48:78-84 Barnes 1989 → Busse WW and Lemansk RF. Asthma. NEJM 2001; 344:350-362.
Andrew Salmon	I could not identify any additional studies needing specific consideration. There is an enormous literature on the platinum-based anti-cancer drugs, but the Report has chosen not to consider these since the subject of concern is those materials to which environmental exposures may occur.

(G3) Please discuss research that you think would be likely to reduce uncertainty in future assessments of halogenated platinum salts and platinum compounds.

Raymond Biagini	Powerfully designed prospective epidemiologic studies including personal sampling such that the sensitizing exposure concentrations, Pt speciation and aerosol particulate sizes can be ascertained with great confidence.
George Cherian	Most of the published epidemiological studies are based on occupational exposure to halogenated platinum salts in refineries and catalyst production plants. Studies should be designed to measure the exposure levels frequently in air and individual worker exposure with health effects such as allergic sensitization. The speciation of platinum compounds is also essential because even in halogenated compounds the health effect may vary depending on the number of halogen atoms and the type (chlorine, bromine and iodine). Since general population is not exposed to halogenated platinum salts in the environment, these measurements are only relevant to occupational exposure. The major form of platinum in the environment is the emission from automobiles with catalytic converts, and this form of platinum is insoluble oxidized platinum that does not have any toxicity. Therefore, the major concern of platinum exposure is at occupational environment. It is essential to determine the exposure of different forms of platinum levels in general population.
Rogene Henderson	I do not know that more research is needed to determine an RfD, because apparently people are not usually exposed to platinum compounds by the oral route. A section on potential oral exposures would help clarify this. The exception is the use of platinum compounds as chemotherapeutic agents. In that case, the main concern is to determine the dose that will be effective against cancer without killing the patient. More research information would be helpful in setting the RfC. Studies that included more extensive histopathology would help determine if there are target toxicities other than the kidney and the development of allergic sensitivity to Pt. No studies have been conducted for the effect of platinum compounds on reproductive or developmental endpoints. We still need information on how much of an exposure is needed to develop allergic sensitization, and how variable this is among individuals. Is the sensitization related more to exposure concentration or to number of repeated exposures or both? Such information would help in setting an RfC protective against sensitization.
Kenneth Rosenman	Animal studies using different platinum compounds and dosages with allergic sensitization as the outcome are needed to address the allergenic potency of different platinum compounds. A true longitudinal occupational health study which assessed individuals at time of employment not when they had already been working for years, included periodic follow-up, determined why individuals left employment and accurately assessed levels of exposure of specific platinum compounds would be useful.
Andrew Salmon	As noted in the Review, there is a lack of studies addressing the oral toxicity of platinum salts. Those that have been reported are limited by a failure to properly identify toxic

endpoints by detailed methods such as histopathology, a lack of dose-response information due to insufficient number of dose levels, and/or inadequate description of the study designs and results in the available reports. There is however, sufficient information to suggest that kidney toxicity is an endpoint of concern following oral exposures to various soluble platinum salts, and it would be desirable to characterize this more thoroughly as regards dose-response, histological findings and the relative potency of different platinum salts.

Although the key study used as the basis for the derivation of the RfC is a suitable basis for dose-response assessment, there are some problems with the range of exposure levels studied and the way in which these were measured and reported. Daily variations in exposure levels were considerable, and the exposed groups were limited to two with widely different exposures. If additional work were possible either with this or with another cohort, it would be worth developing additional exposure measures, ideally including more extensive and ongoing personal exposure measurements. The aim would be to provide improved resolution in the dose-response assessment, which is currently quite crude and relies on a LOAEL/NOAEL determination. Some other studies of occupational exposures to toxic metals and other elements have successfully used biomonitoring to estimate both short- and long-term exposures. Although serum levels have been shown not to be reliable indicators, it might be possible to identify other biomarkers for platinum exposure. Although the exposure levels of interest are low, the non-exposed background is several orders of magnitude lower still. This approach might also be useful in comparing actual absorbed platinum levels following exposure to materials or mixtures other than hexachloroplatinates.

Assessment of health endpoints responsive to IgG responses, in addition to the SPT which primarily addresses IgE response, would also be useful if such tests could be developed. This may be of interest; evidently the correlation between SPT results and bronchial challenge responses in the various studies is good although not absolute.

Further clarification of the carcinogenic potential of platinum compounds would be helpful. Ideally, there would be experimental confirmation of the assumption that the carcinogenic effect of the platinum-based anticancer drugs is not shared by halogenated platinum salts or other Pt compounds, by means of a bioassay including appropriate dose levels of key compounds. Further mechanistic investigations of the carcinogenic properties of cisplatin might also help to further illuminate this question.

(G4) Please comment on the identification and characterization of sources of uncertainty in Sections 5 and 6 of the assessment document. Please comment on whether the key sources of uncertainty have been adequately discussed. Have the choices and assumptions made in the discussion of uncertainty been transparently and objectively described? Has the impact of the uncertainty on the assessment been transparently and objectively described?

Raymond Biagini

Merget et al., 2000 was used as the principal study for the derivation of the chronic RfC. Pt-specific allergic sensitization, as measured by the development of a positive SPT, was selected as the critical effect resulting from exposure to halogenated Pt salts. No cases of sensitization developed during the 5-year period in 111 workers (persistent and intermittent low-exposure groups) who worked in areas with reported median air concentrations of 0.0066 µg soluble Pt/m3 in 1992 and 0.0004 µg soluble Pt/m3 in 1993. Exposure in the low-exposure group (persistent and intermittent) was considered the NOAEL. Area sampling for Pt exposure rather than personal sampling was used as the basis of the NOAEL. There was limited personal sampling performed. A total UF of 1,000 was applied to derive the RfC: 10 for consideration of inter-individual variability (UFH: human variability), 10 for extrapolation from a subchronic study (UFS), and 10 for database deficiencies (UFD). The only assumption which hasn't been addressed is that exposures were in a catalyst production facility, which may lead to totally different outcomes when compared to other exposures.

George Cherian

There are critical deficiencies in the data base on the toxicity of platinum compounds because of limited studies that can provide useful information for dose-response analysis. Animal studies suggest that kidney is a potential target organ for the toxicity of soluble and insoluble platinum compounds and anti-cancer drug, cisplatin.

However, the limited available data are insufficient to characterize the type of renal toxicity and analysis of dose/response relations. Derivation of RfD based on nephrotoxicity from limited data would result in a cumulative uncertainty factor of 10,000 or greater (database, subchronic to chronic, LOAEL to NOAEL, animal to human & human variation, etc). Therefore, an oral RfD for platinum compounds was not derived in the draft document. I agree with this conclusion.

The critical effect of inhalation of halogenated platinum salts in both animal and human is allergic sensitization. Occupational exposure to halogenated platinum salts can result in allergic asthma, rhinitis, cough, wheeze and dyspnoea. In most of these studies, allergic sensitization is observed after exposure to halogenated platinum salts but a complex mixture of halogenated platinum salts may be formed during refining. A five year follow up study in German platinum refinery workers (Merget et al 2000) provides data on NOAEL, exposure levels and incidence of allergic sensitization after exposure to halogenated platinum salts. This prospective cohort study was used as the principal study for the derivation of the chronic RfC for platinum compounds in this EPA draft. The arithmetic mean exposure level of the low exposure group of 3.37 ng soluble Pt/m3 represented the NOAEL in this study and was used to derive the POD for the development of an RfC for halogenated platinum salts.

The authors of the draft review have used a total uncertainty factor of 1000 to POD to derive the RfC for general population from the occupational exposure data of halogenated platinum salts. A default factor of 10 was used to account for variation in susceptibility of human population, a factor of 10 was used to account for uncertainty in extrapolation from subchronic to chronic and a factor of 10 was used for deficiencies in platinum database. All these uncertainty factors are arbitory numbers selected without any

scientific reasons, and should be explained.

I consider that there are few flaws in the assumption that the data from occupational exposure of halogenated platinum salts can be used to derive RfC for general population who are not normally exposed to halogenated platinum salts in the environment. In general population, the major exposure of platinum is from the automobile exhaust emission from catalytic converters. The form of platinum in this emission is mainly oxides of platinum either as soluble or insoluble form. These forms of platinum compounds are inert and do not show any allergic sensitization. Therefore, it is difficult to justify that the occupational exposure form of halogenated platinum salts can be applied directly to exposure forms in general population. Thus, I cannot agree that this particular approach to use the data from occupational exposure form of halogenated platinum salts and its response of allergic sensitization to calculate RfC for general population is scientifically correct or provide any useful information. The exposure of platinum compounds in the environment should be monitored first.

Rogene Henderson

I found the listing and description of the uncertainties associated with the development of the RfC to be transparent and objective. The effect of the uncertainties on the RfC value was discussed. But there was one uncertainty that was left out, I think, and which would greatly affect the RfC. That uncertainty relates to how long or how many repeated exposures are required to develop allergic sensitization to Pt compounds. The document clearly points out that we do not have this piece of information and some sensitization may occur after relatively short periods of exposure.

The allergic sensitization effect is the basis for the POD for the setting of the RfC and despite this, an uncertainty factor of 10 is used to account for use of a subchronic study. This does not seem appropriate because the endpoint used does not require a chronic exposure to develop. The safety factor of 10 for use of a subchronic study is usually used for animal studies, but should not apply to human epidemiology studies. <u>I think this is a major flaw in the analysis.</u>

Kenneth Rosenman

Four additional issues of uncertainty to add are: 1) Is skin prick test the most sensitive or too sensitive an outcome. Not all individuals who are allergic to platinum are skin prick test (SPT) positive. There is limited data from Brooks that bronchial hyperresponsiveness precedes a positive SPT. There is evidence for platinum and other substances that there are other pathways for developing asthma that do not involve IgE/skin prick positive test. On the flip side, some individuals may have a positive skin test and never develop clinical symptoms. This would make SPT too sensitive, a marker of exposure but not an adverse health effect. 2) No true longitudinal study that assesses individuals prior to first exposure; 3) Workplace pre-placement exams may exclude individuals at increased risk (i.e. atopics); 4) There is some evidence that respiratory sensitization can occur from skin exposure.

Andrew Salmon

Key sources of uncertainty are adequately discussed, and the basis of the choices made to address these uncertainties in the risk assessment has been described. These sections of the Review are thorough and clearly written, laying out the considerable uncertainties involved in derivation of the value for the RfC and the necessity of using data in which the level of confidence is relatively low, for want of better data. Although the Review does address the impact of uncertainty as to the relevance, or otherwise, of carcinogenicity data on Pt-based anticancer drugs to Pt compounds likely to be found in the environment, the treatment of this topic is not as comprehensive as the consideration of the non-cancer effects. A further issue which is briefly addressed but might benefit from further exploration (and is certainly a data gap inviting further research) is the question of what Pt compounds are actually released into the environment either from industrial sources or from fuels and automobile catalysts. In addition, there seems to be some uncertainty as to the extent to which such materials, whatever they are, may be converted *in vivo* to more bioavailable, and possibly more toxic, forms after oral uptake or inhalation. These questions, although probably without a clear answer at the present time, have a major impact on the usefulness of the RfC outside of the occupational context of the studies in which it is based. Treatment of the uncertainty over the possibility of a carcinogenic effect of platinum compounds (other than cisplatin – a probable human carcinogen) is very limited. This is to a considerable extent a consequence of the inadequacy of the data to define this issue, but a little more effort to at least define the problem would be helpful.

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Reviewer Post-Meeting Comments: Chemical-Specific Questions

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(A) Oral reference dose (RfD) for halogenated platinum salts and platinum compounds

(A1) An RfD was not derived due to lack of adequate data to characterize the health effects associated with oral exposure to halogenated platinum salts and platinum compounds. Are you aware of any data that might support development of an RfD for halogenated platinum salts and platinum compounds?

Raymond Biagini	No. I do not know of any data which might support RfD for halogenated platinum salts and platinum compounds.
George Cherian	There are no adequate studies on oral exposure to halogenated platinum salts and compounds and their health effects. Therefore, I agree with the authors that there is no data available to calculate RfD for halogenated platinum salts and other platinum compounds.
Rogene Henderson	No, I know of no such data. I agree with the authors on not trying to develop an RfD based on inadequate data.
Kenneth Rosenman	No.
Andrew Salmon	No. This is a key data gap, as noted in my earlier comment on research needs.

(B) Inhalation reference concentration (RfC) for halogenated platinum salts and platinum compounds.

(B1) The Merget el al. (2000) occupational epidemiological study was selected as the basis for the RfC. Please provide a detailed explanation of any strengths or weaknesses regarding the Merget et al. (2000) study that are not identified or adequately reviewed in the current assessment. Please comment on whether the selection of this study was the principal study is scientifically justified. Has the rationale for this selection been transparently and objectively described in the document? Please identify and provide the rationale for any other studies that should be selected as the principal study.

Raymond Biagini	The Merget et al. (2000) study was performed in a catalyst production plant where the Pt salt solution is prepared in a closed system and is then brought to an impregnation area where different substrates are immersed in the Pt salt solution by robots. I would presume that the Pt salt solution is adsorbed to these substrates, possibly modifying the aerodynamic diameter and respirability of the resultant aerosol(s). No measurements of aerodynamic diameters of the aerosols were presented in the paper. If the aerosols had larger diameters, the respirability and personal Pt exposures would be reduced. The method for detection of Pt doesn't account for the identity of the Pt salt actually measured. The identity of the actual Pt salts and the lack of aerodynamic measurements are weaknesses in the Merget study. From a strictly scientific standpoint, the Merget study would not be appropriate to base a standard for exposure to halogenated platinum salts.
George Cherian	The five year occupational epidemiological study in German platinum refinery plant (Merget et.al 2000) has several strength and weakness to calculate the RfC for occupational exposure. This study is designed to evaluate the exposure levels of halogenated platinum salts and its health effects in workers at a platinum refinery plant. This prospective study provides an exposure estimate that represents a NOAEL of 3.37 ng soluble Pt/ m3 at which no adverse effect of allergic sensitization to halogenated platinum salts will develop over 5 year period. The major weakness are the lack of speciation of the soluble platinum measured in air and only 3 exposure groups with marginal adequacy for BMD modeling. Since 46% of workers in the high exposure group are smokers, it may be necessary to apply a factor to calculate the LOAEL in this study. The selection of this study is scientifically sound to measure NOAEL and LOAEL at work place. There are no other studies that describe both the exposure levels of platinum compounds and health effects.
Rogene Henderson	I agree with the selection of the critical study (Merget et al., 2000) The work done by Merget et al. is the appropriate choice for the analysis. A strength is the availability of exposure data. A weakness is that only one level (high) gave a positive response. In selecting an RfC for an exposure that induces allergic sensitization as its major adverse health effect, it is important to define how high an exposure concentration is required to increase the incidence of sensitization. The Merget et al (2000) study is important, in that it provides an exposure level that did not produce sensitization and a concentration that did increase the incidence of sensitization. One would like to have a larger number in each exposure group but over 100 in the high and low groups is a reasonable sample.

	Also, the exposures were highly variable within each group, and one does know if the sensitized individuals had higher or more repeated exposures than those in the group that did not become sensitized.
Kenneth Rosenman	Two additional weaknesses of the Merget study are: 1) Lack of discussion of components of pre-placement exams provided to workers and possible exclusion of individuals at increased risk of developing platinum allergy; and 2) Lack of discussion that a certain percentage of cohort were already working at entry in the study and was a "survivor" population with those who developing allergy in the first couple of years of exposure (typical time for developing such a reaction) having already left the cohort. The effect of both these additional weaknesses would be to underestimate the rate of allergic sensitization in this population. The rationale for selecting Merget study has been well documented and justified and there is no justification for selecting an alternative study.
Andrew Salmon	Selection of the Merget et al. (2000) study as the basis of the RfC is justified since of all those available this one provides the best information on the nature and extent of the exposure to halogenated platinum compounds, and the best opportunity to define the dose-response relationship for the sensitization response, which is clearly the critical effect for human inhalation exposure to the halogenated platinum salts. This rationale was well described in the report. Although this study does present the best available opportunity to characterize the dose-response relationship, there are some definite weaknesses nevertheless, which are explored in the Review. These include the considerable variability in the exposure measurements, which the Review examines in detail to evaluate the best way to describe the exposures of each group of workers for risk assessment purposes. See also the comment below on BMD vs NOAEL analysis.

(B2) Pt-specific allergic sensitization, as measured by the development of a positive skin prick test (SPT), was selected as the critical effect for the RfC resulting from exposure to halogenated platinum salts. Please comment on whether the selection of this critical effect is scientifically justified. Is the rationale for this selection transparently and objectively described in the document? Please provide a detailed explanation. Please comment on EPA's rationale regarding adversity of the critical effect. Has it been objectively and transparently described and is it supported by the available data and your understanding of the available scientific data. Please identify and provide the rationales for any other endpoints that should be considered in the selection of the critical effect.

Raymond Biagini	Pt-specific allergic sensitization, as measured by the development of a positive skin prick test is a valid critical effect for the RfC.
George Cherian	Platinum specific allergic sensitization was measured by the development of a positive skin prick test (SPT), and the authors have described well its use as a critical effect to measure the health effects of exposure to halogenated platinum salts. From the published data, this may be the best critical health effect to monitor for inhalation of halogenated platinum salts. For other forms of platinum compounds, preliminary studies suggest that kidney may be a critical organ; but there is little information on the type of renal damage or the dose required to cause renal damage.
Rogene Henderson	I agree with the selection of the allergic sensitization endpoint as the critical effect. It is well justified in the document. It is also the endpoint that is well known to occur and cause problems in occupational settings. It would be a mistake not to choose this as the critical endpoint. In industry, sensitization is considered a major occupational problem and permissible exposure levels are set quite low to prevent the need to remove sensitized workers from the area.
Kenneth Rosenman	Selection of SPT is scientifically justified. On one hand it may not be sensitive enough or too sensitive (see response G-4). On the other hand, it is the most common outcome measured and it is an objective outcome unlike symptoms. Potentially some combination of respiratory symptoms and measurement of hyperreactivity could be used, which would be considered a true adverse health outcome.
Andrew Salmon	This is a well-established test which has been used extensively in clinical and epidemiological studies of immune sensitization, and is established as an indicator of IgE type reactions. Although there are indications that other types of response (IgG based for instance) may also occur following exposure to halogenated platinum salts, the strong correlation between SPT positive responses and measurable responses in bronchial challenge test both for this and for other antigens establishes this test as a reliable indicator of an adverse health effect. This is satisfactorily explored and explained in the Review. Allergic sensitization to halogenated platinum salts is a widely reported response with known severe adverse effects, and is considered sufficiently serious that workers who become sensitized are generally terminated or moved to jobs where exposure to halogenated platinum salts does not occur.

(B3) The RfC was quantified for halogenated Pt salts from the Merget et al. (2000) occupational epidemiological study which provided exposure data from airborne soluble Pt measurements that were not further characterized for specific Pt compounds. Please comment on the scientific justification of the derivation of an RfC for halogenated Pt salts from measurements of airborne soluble Pt that were not further characterized for specific Pt compounds. Please identify and provide the rationale for any other approaches that should be considered in the derivation of an RfC for Pt compounds.

Raymond Biagini	The Pt was most probably adsorbed to catalyst matrices as pointed out above. It was never pointed out in the paper if the workers had exposure to hexachloroplatinic acid or some other Pt compound. If exposure was to non-chlorinated Pt species, results for hexachloroplatinic acid skin tests would be compromised. Speciation of exact exposures would have been helpful.
George Cherian	The lack of speciation of the soluble form of platinum in air measurements is a major weakness of the Merget et.al 2000 occupational epidemiology study. It is known that the number of chlorine atoms can affect the allergic sensitization, and other halogens such as bromine and iodine may decrease the effect. Thus exposure to other halogenated compounds along with chlorinated platinum salts may not provide an accurate measurement of dose required for health effects.
Rogene Henderson	I think the approach was appropriate because no better data were available.
Kenneth Rosenman	Quantifying the RFC for halogenated platinum salts since the weight of the scientific knowledge is that these salts are clearly allergens. The use of other platinum measures would add additional uncertainty.
Andrew Salmon	This limitation of the exposure measurements is apparently an unavoidable consequence of the available measurement methods. In the case of the catalyst production workers studied by Merget et al., the sources of the exposure would necessarily have been specific more-or-less pure chemicals, so it is not unreasonable to assume that the nature of the source materials defines the nature of the exposure. From the description in the Review it would appear that the soluble platinum compound being handled in the plant studied by Merget et al. is specifically hexachloroplatinic acid and/or its salts; if this is the case then the reliance on soluble platinum determinations as the exposure measure is justified. However, it does appear that some other catalyst manufacturing operations did handle other soluble materials, including tetraamine platinum dichloride (a soluble salt but not a "halogenated Pt Salt" as defined for these purposes). It would be useful for the Review to more explicitly clarify whether or not such materials were ever handled by the workers studies by Merget et al., or could have been included in the air samples taken. Obviously this issue is more of a problem in determining the exposures of refinery workers who might be handling a broader range of materials including some with a less well-defined composition. It is also a key problem in determining the usefulness of the RfC for protecting the population at large from environmental platinum exposures, where the nature of the small proportion of the ambient material which is soluble appears to be

unknown (but may well not be hexachloroplatinate?).

(B4) Is the statement that "The use of the RfC for Pt compounds other than halogenated Pt salts is not recommended as the similarity between these compounds and other soluble forms of Pt compounds is unknown" scientifically justified? Please identify and provide the rationale for any other characterization of the platinum compounds that are relevant to the recommended use of the RfC.

Raymond Biagini	This statement is supported by the existing literature. Halogenated Pt salts appear to be the sensitizing compounds with the extent of halogenation appearing to affect the sensitizing capability.
George Cherian	The limited studies on soluble and insoluble platinum compounds other than halogenated platinum salts suggest that they may have different health effects such as toxicity to kidney or liver. Thus there is little similarity between the health effects of different platinum compounds. The reactivity of ionic form of halogenated platinum salts with proteins is an important property to form Pt-specific immune response where small atoms such as platinum will act as haptens by binding with larger endogenous substances. The other forms of platinum cannot interact with these molecules and thus cannot generate any immune response. Thus, they are not considered as toxic as halogenated platinum salts at workplace.
Rogene Henderson	The calculation of the RfC was based on a health effect that is associated only with soluble forms of halogenated platinates. Therefore the RfC is only applicable for soluble halogenated platinates. This fact also indicates how important it is to have a section on the potential for environmental exposures to these compounds. If the potential is nil, that should be stated.
Kenneth Rosenman	Yes.
Andrew Salmon	This statement does appear to be justified. As noted below, the review presents evidence that the sensitization effect upon which the RfC is based is specific to the halogenated Pt salts. It would certainly be useful to have alternative health-based standards which could be applied to soluble Pt compounds other than these halogenated salts, but there do not appear to be any data available on which to base such standards at present. One is tempted to suppose that it would be useful to have a non-halogenated soluble Pt standard addressing the kidney effects reported for oral Pt exposures, but clearly there are no data sufficient to develop such a standard for either the oral or the inhalation route. This does however present a significant problem and raises the question of exactly how useful the RfC is going to be in practice. There may be situations where non-occupational exposures to halogenated Pt salts occur as a result of release of materials from accidents, contaminated sites, or industrial facilities, but it appears that to date the main area of concern for these compounds is occupational exposure which is regulated by OSHA rather than EPA. The environmental exposures of concern apparently relate primarily to platinum release from automobile catalysts and fuel additives. While it appears to be unknown at this point what chemical forms comprise these emissions (and deposited dust derived therefrom), there does not appear to be any obvious reason to expect these to be

composed of chloroplatinates or other halogenated materials. So we are left with the uncomfortable situation that there is still no agreed standard against which to evaluate such exposures.

One might argue that a "screening" approach to the problem would be to use the RfC presented here anyway, recognizing that the standard is not strictly applicable but that such a comparison would be at least health protective (since sensitization appears to be the response with the lowest effective dose). A conclusion of no hazard on this basis would be at least somewhat reassuring. Although any prediction of significant hazard would be questionable, it might be useful as an indication that further investigation is imperative and that a precautionary approach is appropriate. However, even the assumption that sensitization is the critical effect at low doses is somewhat uncertain given the lack of dose-response information for other effects (neurotoxicity, developmental toxicity, kidney effects) and the limited understanding of long-term toxicokinetics of Pt compounds other than drugs.

(B5) EPA has concluded that the allergenic activity of Pt is compound-dependent and sensitization effects appear to be restricted to the halogenated Pt salts. Please comment on whether this finding is justified and supported by the scientific evidence.

Raymond Biagini	See answer to question B-4.
George Cherian	As described in B-4, the ionic forms of halogenated platinum salts have a specific interaction with proteins that may result in immune response and release of histamines and allergic sensitization. The other forms of platinum compounds may not be even absorbed actively and enter the cell, and thus may be somewhat inert. The *in vitro* and animal studies partly support this hypothesis. Thus the allergic sensitization reactions are specific to halogenated platinum salts formed during processing of platinum catalyst and refining platinum compounds.
Rogene Henderson	I agree that the data indicate that the property of inducing allergic sensitization is associated with platinum compounds that have halogen-ligands coordinated with platinum. This health effect is not associated with platinum halides when the halide is present in ionic form.
Kenneth Rosenman	Certainly there is uncertainty in this statement and further research in an animal model with the differing platinum compounds is clearly warranted. Given the potential for extensive population exposure, this testing is certainly indicated for the form of platinum exhausted from vehicles with platinum containing catalytic converters. Further discussion of the chemistry and transformation of platinum compounds would be useful.
Andrew Salmon	The report reviews various lines of evidence showing that the allergic sensitization effect is specific to the class of compounds identified as "halogenated Pt salts". The study by Linnett and Hughes (1999) described on page 53 *et seq*. which contrasted the effects on workers of exposure to chloroplatinates and to tetraamine Pt dichloride is particularly informative in this regard. There is a low prevalence of sensitization (3%) in workers exposed to tetraamine Pt dichloride "only", as opposed to those with an exposure which included chloroplatinates (39% for refinery workers). This suggests that the few cases seen may be as readily attributable to accidental cross-contamination or job misclassification as to any sensitization effect of the non-halogenated Pt salt. This conclusion is supported by other epidemiological investigations, and by the studies of sensitization in mice by Schuppe et al (1992, 1997b) showing sensitization following exposure to hexachloroplatinates but not to tetraamine Pt dichloride. Cleare et al. (1976) also reported that insoluble Pt compounds and $K_2[PT(NO_2)_4]$ did not elicit positive SPT responses in platinum workers.

(B6) The Merget et al. (2000) study reported 13/115 workers in the high exposure group developed Pt-specific allergic sensitization (as determined by a positive SPT) during the 5-year study period. The Merget et al. (2000) study did not adjust its reporting of SPT positive individuals for smoking as a risk factor for developing Pt-specific allergic sensitization. Please provide comments on the potential impact of this approach and implications it may have for the RfC derived from this study.

Raymond Biagini	Smoking has been associated as a positive risk factor for sensitization to halogenated Pt salts. The lack of control for smoking could lead to an incorrect estimation of the RfC.
George Cherian	Smoking was identified as a risk factor in the development of allergic sensitization in several occupational studies of workers in platinum refinery and catalyst production plants. However, non-smokers also develop allergic sensitization to halogenated platinum salts in the same occupational environment. Few studies suggest that the prevalence of developing allergic sensitization in smokers may be about 4.6 times as compared to non-smokers. But the major effect of smoking may be to decrease the time lag for developing allergic sensitization in platinum workers. Thus, Venable et.al (1989) reported that there was 75% probability of non-smokers developing allergic sensitization in 3 years of exposure while smokers can develop allergic sensitization in one year at the same probability. Thus, it appears that smoking can enhance the time of appearance of allergic sensitization in workers exposed to halogenated platinum salts. There is no discussion whether smokers can develop allergic sensitization at a lower dose of halogenated platinum salts exposure than non-smokers. This may be an important point to rule out. Thus smoking may have an additive effect in the development of allergic sensitization in platinum workers. Merget et al 2000 study does not adjust for smoking for allergic sensitization in halogenated platinum salts exposed workers in refinery plant. The authors of the draft review describe (p 142) that adjustment for smoking as a risk factor may result in a reduced incidence of workers with platinum specific allergic sensitization; however it is unlikely that it would affect the exposure level of high dose as a LOAEL for platinum, This is correct only if smoking decrease the time of appearance of allergic sensitization and not the exposed dose of halogenated platinum.
Rogene Henderson	One might consider the smoking population as a sensitive subpopulation. Since the RfC is supposed to protect sensitive subpopulations, I have no problem with smokers being included in the study.
Kenneth Rosenman	The data on smoking is that individuals become sensitized sooner, not at a higher incidence. Therefore, no adjustment is indicated. Even if smoking rates have come down over time there are still smokers in the general population. Also the RFC is based on the NOAEL (people who did not become sensitized), which would not be effected by adjusting for cigarette smoking. Additionally there are smokers in the general populations and the general population is exposed to the ambient pollutants, ozone and particulate, that potentially increases the effect of allergens.
Andrew Salmon	Since the intention of the RfC is to protect members of the population at large (which includes smokers), it is not unreasonable to include smokers in the population studied to

determine the impact of halogenated Pt salt exposures. Some uncertainty is potentially introduced into the overall conclusion by the fact that smoking is a risk factor for Pt sensitization. However, in this particular case if smoking status had been included in the analysis it would not have affected to overall conclusion. Supposing for the sake of argument that the "smoking-adjusted" incidence of sensitization in the high-exposure group was 10/115 as opposed to 13/115. This would not affect the determination of the NOAEL in any way, since there would still be a low exposure group, defining the NOAEL, with no sensitized workers and a high exposure group with a significant number sensitized which defines the LOAEL. The only way that such an adjustment would affect this calculation is if the effect of smoking so great as to bring the statistical significance of the effect in non-smokers into question: there is no indication that this is so. (The Review summarizes this point, that adjusting for smokers would not affect the overall derivation of the RfC.) This consideration of smoking as a modifying factor is distinct from the situation if the SPT data were sufficient to allow estimation of an actual dose-response curve, where the curve shape and slope can be determined and used in estimating a POD. Here changes in the slope of the curve, or its threshold, as a result of modifying factors might indicate a different POD for smokers and non-smokers. Unfortunately this analysis is not possible with the data from Merget et al. (2000), illustrating both the limitations of those data and the inherent lack of precision in the LOAEL/NOAEL methodology.

(B7) The RfC was derived on the basis that chronic exposure at the dose level would not induce allergic sensitization. However, it is unknown if the RfC would be protective of exacerbation of symptoms in individuals previously sensitized to halogenated platinum salts. Please comment on whether the decision not to derive an RfC based upon elicitation of an allergic response as the critical effect is scientifically sound and has been transparently and objectively described in the document.

Raymond Biagini	Elicitation of allergic effects normally occurs at levels much lower than concentrations which sensitize. The RfC would most probably not be protective for symptoms in an already sensitized individual. Pt sensitization, once induced appears to be long-lasting with evidence of sensitization to very low levels of Pt years after apparent cessation of exposure.
George Cherian	A few of the workers who showed allergic sensitization in the cohort of Merget et al 2000 study were previously exposed to halogenated platinum salts in their previous employment. The time required to develop allergic sensitization is likely depend on exposure dose, frequency of exposure and biological-half time of the allergen as well as individual variation. It is still unclear whether previous exposure to halogenated platinum salts can make a worker more susceptible or resistant to subsequent exposure in allergic sensitization.
Rogene Henderson	This question brings up a basic problem with having an allergic response as the primary health effect of interest. There can be no doubt that the major health effect of concern in exposures to halogenated platinum compounds is the development of allergic sensitization. But that means there are two exposure concentrations of concern. One is the concentration and the number of exposure times to induce the initial sensitization. The second is the concentration required to elicit an allergic response in a sensitized person. I think the most important task is to set a concentration that will not elicit the initial sensitization. If the sensitization can be prevented, one does not have to worry about the concentration that elicits a response in a sensitized person. So I think it is appropriate to set the RfC for the public at a level that would not be expected to induce sensitization.
Kenneth Rosenman	First, there was inadequate data to derive an RFC based on elicitation of an effect in previously sensitized individuals. Second, derivation of a level to protect against inducement of an allergic sensitization is an appropriate public health outcome if such a level was effective then sensitization would not occur and there would be no need for a second even lower value. Based on what is done on individuals sensitized to different chemicals, on would need a RFC of zero to protect already sensitized individuals I am not aware of any standards that have been developed to protect previously sensitized individuals.
Andrew Salmon	This decision is implied rather than extensively described and defended in the document. A summary of the limited knowledge of the relationship between exposure levels causing sensitization and those eliciting a response in sensitized individuals appears in Section 4.6.3.1.7 (page 124). The key problem with basing an RfC on the response of sensitized

individuals to halogenated Pt salts is that the data on which to base such a value are very limited and hugely variable. Thus Biagini et al (1985a) report that sensitized individuals show positive SPT responses at concentrations between 3 and 6 orders of magnitude lower than non-sensitized individuals: although data appear to be lacking it would not be unreasonable to assume that the variation in levels producing bronchoconstriction, rhinitis etc. would be at least as variable. It is also unlikely that such data could be obtained. A large number of subjects would be needed to obtain a statistically reasonable estimate in the face of such variability, and given that platinum handling of any type is not among the most frequent occupational descriptions such a study population would be hard to assemble. Actual dose-response determination even for SPT testing, let alone FEV_1 measurements, would be considerably more involved than the simple responder/nonresponder classification used in most published studies, and there is a significant question as to whether such investigations would be approved by an institutional review board, even if they were affordable.

The decision to use induction of sensitization rather than the response of sensitive individuals is thus more or less forced by the availability of data. One could, however, argue that in the light of this decision the choice of a UF of 10 to deal with inter-individual variability is insufficient to protect sensitized individuals – according to Biagini et al (1985a) a UF of at least 10^3 would be needed. However, use oif such a large UF for this one extrapolation would put the overall UF into a range where the RfC would be regarded as unreliable and unusable. Also, the RfC is generally defined as a level which is protective of "most" of the members of the general population: very rare idiosyncratic responses are specifically not included. Since occupation as a platinum worker is a very rare characteristic in the general population, and the responses of such individuals are highly variable even within that class, it is not unreasonable to regard the sensitized worker as an "idiosyncratic" individual, and not to include such individuals in the RfC. However, if it were to be established that sensitizing exposures were likely in the general population (e.g. from fuels or emissions from automobile catalysts), it would be necessary to address this concern in some way. This might be a particular concern if platinum-containing fuels became more widespread (and that a component of these additives or emissions were allergenic), since in theory these might provide a more concentrated exposure in the event of accidental spillage or mishandling. In this case there is no reason to assume that dermal or oral exposure would not act as a sensitizing stimulus for subsequent low-level reactions to inhaled platinum salts.

(B8) A NOAEL/LOAEL approach was applied to incidence data for Pt-specific allergic sensitization to derive the POD for the RfC. The available data are of marginal adequacy for BMD modeling because only three exposure groups (high, low, and no exposure) are available and only one of these groups has a non-zero response. However, BMD modeling was applied to incidence data for Pt-specific allergic sensitization for comparative purposes. Please provide comments with regard to whether the NOAEL approach is the best approach for determining the POD. Have the NOAEL approach and the BMD modeling approach been appropriately conducted and objectively and transparently described? Please identify and provide rationales for any alternative approaches (including BMR, model, etc.) for the determination of the POD and discuss whether such approaches are preferred to EPA's approach.

Raymond Biagini	Basing the NOAEL on one study, albeit well done, with questions with regard to combination exposure (catalyst production facility) might not be the most conservative approach. I agree that the available data are of marginal adequacy for BMD modeling. I have no recommendations as to another model approach.
George Cherian	Since the selected principle study, Merget et al 2000 had only three different levels of exposure groups of halogenated platinum salts (no exposure, low exposure & high exposure), it is difficult to use BMD modeling for analysis. Therefore a NOAEL/LOAEL approach was used to derive the POD for the RfC. I believe that this is the only approach possible with the limited test groups and exposure data collected. These data are useful to calculate NOAEL and LOAEL for halogenated platinum salts in occupation exposured people in platinum refinery plants. But these data are not appropriate to calculate RfC in general population who are not exposed to halogenated platinum salts in the environment...
Rogene Henderson	I think the approach was appropriate considering the scarcity of data.
Kenneth Rosenman	The derived benchmark dose is not adequately presented in the text nor adequately discussed in the context of how it differs from the calculated RFC.
Andrew Salmon	As noted briefly in the main report, and explored more thoroughly in the appendix, the data from the study by Merget et al. (2000) are not really suitable for benchmark dose analysis because there is only one exposure group or which the response rate is above zero. This provides no information on the true shape of the dose response curve, and only mildly constrains the location of the (assumed) threshold. No combination of choices within the BMD evaluation (BMR, model etc.) would alter this deficiency. Under these circumstances, the NOAEL/LOAEL approach is the better choice. However, it is notable on examination of the dose-response graphs shown in the appendix that there is a considerable separation between the low exposure group (in which there were no responders) and the high exposure group, where there were a substantial number of SPT responses. Thus the true location of the threshold dose for the SPT response is really quite uncertain. Use of the NOAEL/LOAEL approach may in fact therefore identify a POD which is considerably lower than the true threshold. While this uncertainty is at least in the health-protective direction, it illustrates the point that if the data are unsuitable or unsatisfactory for BMD analysis they are in fact likely to provide a very uncertain result by

the NOAEL/LOAEL method also, with the added disadvantage that it is easy to ignore the uncertainty present using the latter approach. The Review correctly identifies the problems with using the BMD analysis, but does not explore the issues which these limitations of the data necessarily present in using the NOAEL as the POD for determination of the RfC.

(B9) Insufficient information is available to predict potential variability in susceptibility among the general population to allergic sensitization from inhaled halogenated Pt salts. Please comment on the transparency, scientific rationale and justification for the use of an uncertainty factor of 10 to account for interindividual variability. Are the criteria and rationale for this selection transparently and objectively described in the document? Please comment on whether the justification for selection of this uncertainty factor based on these data is scientifically justified and transparently described.

Raymond Biagini	As pointed out in the review, the available exposure-response information for the development of allergic sensitization to halogenated Pt salts covers a period of only 5 years, and therefore, a less-than-lifetime exposure duration. In addition, there is a complete lack of information on whether inhalation exposure to halogenated Pt salts or other forms of Pt may induce other systemic, reproductive, developmental, or neurotoxicological effects. In addition, the available occupational data on Pt-specific allergic sensitization are from healthy adult workers (predominately male). The potential susceptibility of young, aged, or asthmatic populations is unknown. The overall confidence in the chronic RfC of low reflects the variation in the exposure data and confidence in the database. These facts are scientifically justified and transparently described.
George Cherian	As stated earlier, the general population is not exposed to halogenated platinum salts in the environment. There are no data on allergic sensitization in a population exposed to other platinum compounds in the environment. Individual differences such as gender are not usually observed in most of the chemical allergic reactions. There is no information on gender differences to allergic sensitization to halogenated platinum salts. Therefore, it is unclear why an uncertainty factor of 10 was selected to correct the individual variation in allergic sensitization in general population.
Rogene Henderson	For an allergic response, one would expect a great deal of variability in the response. The uncertainty factor of 10 was fully justified.
Kenneth Rosenman	The uncertainty factor for differing susceptibility is adequate, although the discussion of childhood susceptibility was not adequate (4.8.1., page 131). Clearly children have a higher prevalence of asthma. Is there data on other substances that children are more susceptible to developing allergic sensitization? If yes then it would be reasonable to include an additional uncertainty factor for children.
Andrew Salmon	The uncertainty factor of 10 to account for interindividual variability (UF_H) is a default policy choice established in the guidelines for derivation of RfCs, rather than a scientific decision based on any particular feature of the specific data considered in deriving the RfC for halogenated Pt salts. As such, there is minimal discussion of the origin of this value in the Review, but there is extensive discussion of how default values for uncertainty factors were selected in various U.S. EPA risk assessment policy documents. The question of whether this default approach is reasonable depends on the assumption, discussed previously in the response to question B-7, that sensitization to halogenated platinum salts is sufficiently rare in the general population that the hypersensitive

response of such a sensitized individual should be regarded as an idiosyncratic response for which it would not be reasonable to expect the RfC to be protective. In this case, there is little in the way of data to suggest the range of variability within the general non-sensitized population, so use of a default is reasonable. One might argue for a somewhat higher value for UF_H (e.g. 30) in order to protect infants and children, who often appear to be more sensitive to effects which predispose to or exacerbate asthma. On the other hand the inclusion of a database uncertainty factor of 10 for lack of sufficient developmental information might also be seen to address this concern. If, by contrast, the intent was to develop an RfC which would protect sensitized individuals, it appears that a UF_H of between 10^3 and 10^6 would be necessary. Since this is to a limited extent based on actual data (Biagini et al., 1985a) it should be seen as accounting for variability rather than uncertainty, so perhaps would not violate the usual limit of an overall UF of 1000 in deriving RfCs. However, it would most likely result in an RfC far below the detection limit. Also, as noted earlier, the assumption that members of the general population are not sensitized to platinum compounds is currently reasonable, although this would need to be re-examined if general environmental exposures to sensitizing compounds were to increase.

(B10) A subchronic study (Merget et al., 2000) was selected as the principal study with allergic sensitization to halogenated Pt salts as the critical effect for the derivation of the RfC. Please comment on the transparency, scientific rationale and justification for the subchronic to chronic uncertainty factor of 10. Are the criteria and rationale for this selection transparently and objectively described in the document?

Raymond Biagini	A database uncertainty factor of 10 for subchronic to chronic uncertainty was applied, noting the extensive support for Pt-specific allergic sensitization in humans as observed in the principal study, and the similar effects observed in animals, but the general lack of toxicity studies on any other endpoint. As stated, the overall confidence in this RfC assessment is low. Confidence in the principal study (Merget et al., 2000) is low. This is transparently and objectively described in the document.
George Cherian	In Merget *et.al* (2000) occupational study, the exposure period was followed for allergic reactions for five years. Most of the allergic sensitization reaction occurred during the first three years in high exposure group in the study. Therefore, in allergic sensitization reactions, it is not the length of time of exposure but the high dose of exposure that is important to initiate the immune response. Therefore, UF of 10 is not justified to extrapolate subchronic to chronic in halogenated platinum salts exposed people where the end point of health effect is allergic sensitization.
Rogene Henderson	I disagree with the use of an uncertainty factor of 10 for going from data from a subchronic study to development of a protective level in a chronic situation. First, the term subchronic is not appropriate for an epidemiology study. Second, there is no indication that development of an allergic condition is dependent on how long one is exposed or on the accumulation of the agent in the body. Allergies can develop after only a few exposures. I do not agree with the use of this uncertainty factor.
Kenneth Rosenman	Yes. The fact that sensitization is more likely within the initial years of exposure makes the inclusion of a protection factor for chronic exposure unnecessary. On the other hand, the point made at the meeting that with ongoing exposure there will be more allergic sensitization and this RFC is meant to protect against a lifetime of exposure would support the inclusion of this uncertainty factor.
Andrew Salmon	The uncertainty factor of 10 to account for subchronic to chronic extrapolation is a default policy choice established in the guidelines for derivation of RfCs. As such, there is minimal discussion of the origin of this value in the Review, but there is extensive discussion of how default values for uncertainty factors were selected in various U.S. EPA risk assessment policy documents. The Review clearly explains the justification for choosing to include this UF in the assessment of halogenated Pt salts, showing that the extent of response (frequency and severity of sensitization) tends to increase with time in workers exposed to these materials. Use of this uncertainty factor when appropriate is recommended in risk assessment guidelines, and it is commonly used in the analysis of both animal and epidemiological studies. A general default assumption for chronic effects is that response is a function of concentration multiplied by the time of exposure. There is considerable uncertainty about how concentration and time relationships affect

immunological responses. There are some indications that the rate of appearance of sensitization responses falls off with time (perhaps because of depletion of the population of sensitive individuals?), but on the other hand there are also indications that lower concentrations may still result in sensitization if exposure is prolonged. In view of these various uncertainties, and the relatively brief duration (five years) of the exposure monitoring period in the key study the use of the subchronic UF is clearly justified.

(B11) An uncertainty factor of 10 was used to account for deficiencies in the halogenated platinum salts and platinum compounds database. The inhalation database currently does not include a chronic, developmental, or a two-generation reproductive toxicity study. Overall, the basic toxicology of halogenated platinum salts and platinum compounds has not been well characterized. Please comment on the transparency, scientific rationale and justification for the selection of the database uncertainty factor. Please comment on whether the application of the database uncertainty factor adequately addresses the lack of toxicity data for halogenated platinum salts and platinum compounds. Are the criteria and rationale for this selection transparently and objectively described in the document?

Raymond Biagini	There is quite a bit of missing information on the basic toxicology of halogenated platinum salts and other Pt compounds. The uncertainty factor of 10 seems reasonable.
George Cherian	The toxicity of halogenated platinum salts and other platinum compounds has not been well characterized, including reproductive toxicity. Thus, there is gap in the database for these compounds. The environmental exposure to these compounds is also small. The major known exposure route of platinum is by inhalation of halogenated platinum at work place of platinum refinery and catalyst production. There may be a use for UF to correct the lack of data base but a large factor such as 10 should be justified. The major problem of the draft document is the attempt to directly extrapolate the exposure levels of halogenated platinum salts in occupational setting and its health effects to general population who are not even exposed to this form of platinum compound in the environment. Moreover, there are no reports on the incidence of halogenated platinum salts induced allergic sensitization in general population.
Rogene Henderson	The use of an uncertainty factor of 10 for the paucity of data was appropriate.
Kenneth Rosenman	I have concern about inclusion of this factor. It is unlikely that the uncertainty in the Merget data causes the NOAEL and the derived RFC to be too high but rather for the NOAEL and the derived RFC to be too low. Accordingly lowering the RFC by a factor 10 would be unnecessary. It was argued at the meeting that this uncertainty factor was for total database uncertainty and the potential for other adverse effects such as developmental toxicity. Given that the RFC is being based on human data with a sensitive outcome that appears to be protective, this additional uncertainty factor does not appear necessary.
Andrew Salmon	Inclusion of this uncertainty factor is standard risk assessment policy when the database does not include a chronic, developmental, or a two-generation reproductive toxicity study, as laid out in the standard U.S. EPA risk assessment policy documents. This is certainly justified by the description of the available data in the Review. (Although there are some minimal developmental toxicity data showing effects on fetal weight, they do not address the requirement for proper evaluation of developmental toxicity.) There are also unanswered questions about the (postnatal) developmental effects of agents impacting the immune system during its formative stages. In this particular case there are additional uncertainties, including the wide variability of the exposure measurements in

the key study, and uncertainties relating to the identity of the material to which workers were exposed in this study, as well as possible differences in potency between different halogenated Pt salts. These are noted in the Review. However, it is important to note that the primary purpose of this uncertainty factor is to recognized deficiency in the database rather than the data, *i.e.* missing classes of information rather than inadequacies of the data which are available. Certainly inclusion of this uncertainty factor acknowledges the presence of these database uncertainties, although the nature of the situation makes it impossible to say with confidence that its value is sufficient to cover all conceivable eventualities: this question can only be resolved by further research.

(C) Carcinogenicity of halogenated platinum salts and platinum compounds

(C1) Under the EPA's 2005 *Guidelines for Carcinogen Risk Assessment* (www.epa.gov/iris/backgr-d.htm), the Agency concluded that there is *inadequate evidence to determine the carcinogenic potential* of halogenated platinum salts and platinum compounds. Please comment on the cancer weight of evidence characterization. Does the lack of available data support the conclusion that there is *inadequate evidence to determine the carcinogenic potential* of halogenated platinum salts and platinum compounds? Has this recommendation been transparently and objectively described in the document?

Raymond Biagini	There is inadequate evidence to determine the carcinogenic potential of halogenated platinum salts and platinum compounds. This recommendation been transparently and objectively described in the document.
George Cherian	Due to inadequate data, there is insuffcient evidence to determine the carcinogenic potential of halogenated platinum salts and other platinum compounds. There is no lifetime animal carcinogenicity bioassay for any platinum compounds. The anticancer drug, cisplatin has been shown to be carcinogen in mice while its analogue transplatin is not. Short-term bioassays for mutagenicity and genotoxicity have shown that two soluble platinum compounds PtCl4 and K2PtCl4 showed positive results. There may be a need to study the carcinogenic potential of certain platinum compounds.
Rogene Henderson	I agree that there is inadequate data to determine the carcinogenic potential of halogenated platinates and platinum compounds.
Kenneth Rosenman	Comments on carcinogenicity are in G-1 and are repeated here: Since cis-platinum has evidence of carcinogenicity and is a platinum compound, the summary statement in 6.2.3 on pg. 164 doesn't adequately represent data. The reason for not discussing possible modes of carcinogenic action (4.7.3, pg. 131) is not adequate.
Andrew Salmon	It is undeniable that the direct evidence available to support an evaluation of the carcinogenicity of halogenated Pt salts is inadequate. However, the Review simply asserts this fact without much further discussion. There are some facts which deserve further consideration, however. First, the Pt anti-cancer drug is classified as a probable human carcinogen, and there are reasons to suspect that many of the other Pt based anti-cancer drugs may share this property. Second, although the insoluble platinum compounds appear to be without effect in genotoxicity assays, a number of positive results have been reported with soluble platinum salts (both halogenated Pt salts and those with other ligands on the platinum). The description of this database as "limited" in Section 5.4 is inappropriate. There are a substantial number of assays reported, and there seems to be a clear rationale in terms of sensitive test systems, solubility of different Pt compounds, and valence state, with which most of the observations are consistent. It is clear that soluble platinum salts have the potential to exert genotoxic effects under appropriate experimental circumstances. This is of course not sufficient to extend the finding to a prediction of carcinogenicity. However given the carcinogenicity finding for

cisplatin, and the lack of either positive or negative direct carcinogenicity observations on other platinum compounds, it could be argued that it would be prudent to assume carcinogenic potential at least for all soluble Pt compounds. However, the authors of the Review chose not to take this approach. There are good reasons which can be advanced as to why it is felt that the positive finding for cisplatin does not extend beyond this class of anticancer drugs. There are also logical mechanistic reasons for predicting that the genotoxicity observed for soluble Pt salts may not be indicative of carcinogenicity. However, the report does not present any of these arguments, simply reiterating that "the data are inadequate". A more thoughtful analysis of those data on Pt salts and anticancer drugs which are available would provide greater confidence in the decision of the Review not to identify a cancer hazard or estimate a cancer risk.

Summary and Conclusions

Raymond Biagini

George Cherian

1. This draft document provides a comprehensive review of published data on platinum compounds. There are only few publications on oral or inhalation exposure of platinum compounds in animals.

2. Most of the information on the health effects of exposure to halogenated platinum salts comes from few of the epidemiological studies on people working in platinum refinery and catalyst production plants. Exposures to soluble halogenated platinum salts have been associated with increased risk of allergic sensitization.

3. Merget, *et.al* (2000) study monitored workers in a German refinery plant for 5 years for exposure levels of halogenated platinum and development of allergic sensitization. This study made only two measurements of soluble platinum in 3 groups of workers who were exposed to no-exposure, low exposure and high exposure of halogenated platinum salts. No speciation of soluble platinum was performed. This study was selected to calculate LOAEL, NOAEL and RfC for halogenated platinum salts in the EPA draft review.

4. Merger, *et.al* (2000) study has provided some information on the health effects of halogenated platinum salts and exposure levels at a platinum refinery plant. But this study has only low confidence because of limited measurement of soluble platinum without any speciation. No correction was made for smoking in this study.

5. The authors have attempted to calculate RfC for platinum in general population from these occupational data on halogenated platinum salts generated during processing of platinum. Since general population is not exposed to halogenated platinum salts in the environment, this is not a good approach to extrapolate the data from occupational exposure of halogenated platinum salts to general population. More data are needed on the type of platinum compounds found in the environment and level of exposure in the general population. It is difficult to calculate any dose/response effect or RfC for general population for platinum without this basic information. The assumptions made in the document to calculate RfC for platinum in general population are flawed and do not have

any good scientific justification.

Rogene Henderson

This document requires the following modifications:

1. Expansion of the section on environmental exposure. Exposure assessment is one of the four major steps in risk assessment (NRC, 1983) but it is given only a brief treatment in this document.

2. The major health risk from exposure to soluble halogenated platinum compounds is development of allergic sensitization. This presents a special problem in assessing risk, because only a few exposures can result in the sensitization. Thus a chronic condition can result from only a few repeated exposures. Chronic exposures are not required to induce the health effect. Thus the use of an uncertainty factor of 10 to go from a so-called "subchronic study" to a chronic exposure is inappropriate.

3. A section should be added that explains the special considerations that are required in developing a risk assessment for an immunologic endpoint and explaining the approach the agency wishes to take. I suggest that the Agency expand the guidance for developing RfC's of RfD's when the critical endpoint is an allergic response. The two areas that I think need special advice (and there may be others) is on the appropriate use of uncertainty factors (especially in going from short term or subchronic studies to chronic studies) and on whether the RfC or RfD is based on protection against initiation of an allergic response or on elicitation of a response in a sensitized person.

4. I am not entirely comfortable with the calculated RfC.

First, I do not agree with one of the uncertainty factors used (see above). On the other hand the UF's for variability and for lack of data may be low.

Second, the level appears to be close to or below the limit of detection for monitoring (See page 63 for LOD reported by Merget (2000): look at Table 2-3 and notice that air samples of 1 or less pg/m3 are rarely reported. In the 1991 WHO IPCS document on platinum, it is stated in one place that the LOD is 0.05 pg/m3 and in another place that it is 0.05 ug/m3. Perhaps different methods of analysis or different sample sizes were used. If the RfC is so low that the required monitoring sample size would not be practical, the RfC would have little value. If there is a practical way to monitor for Pt at a level of 1 pg/m3, correct me. One of the public reviewers suggested that there might be such a method. But this document must definitely discuss the potential methods of monitoring and their LODs in relation to the suggested RfC.

Third, the RfC is for halogenated platinum compounds and apparently there are no data on whether such compounds exist in the environment (as opposed to an occupational setting).

Kenneth Rosenman

Andrew Salmon

The Review is for the most part well-written and already carefully edited: however a few minor issues were noted:

The sentence "Soluble Pt is an operationally-defined fraction of Pt in which many different species can be present … *etc*." first appears on page 3 (para 3, line 3 *et seq*.) but then is repeated verbatim in other locations, e.g. page 17 line 5 and in other subsequent places. Since this isn't a stylistic marvel in the first place it does not merit such enthusiastic use of the cut-and-paste function! Some creative, and location-specific, rewording would be in order.

Page 87, third paragraph, 4 lines from the end: "dorsal route ganglia" should surely be "dorsal <u>root</u> ganglia".

Page 117, numbered paragraph 3, line 7. The sentence "Individuals with halogenated Pt-salt allergic sensitization show a progression of symptom severe asthma with continued exposure" appears to have a grammatical problem: should that be "symptoms of severe asthma" or some such phrase?

A full description of the nasal lavage study by Schins et al. (2004) appears on page 128, in the section on mode of action, but there is also a prior (page 115) reference to this study which does not give any detailed description of the study design or results. A subsequent reference also appears on page 131. This scattered referencing of the same study, especially prior to an actual detailed description, is potentially confusing: the authors should consider re-ordering the study descriptions so a full description appears earlier in the document. Later comments about the study and its implications should note the page where the full description occurs. This also happens to a lesser extent for several other cases.

Page 142, 2nd paragraph, line 13: "Venable et al. (1989)" should read "Venables …" (this citation is correct elsewhere in the same paragraph).

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Appendix A

List of Reviewers

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Peer Review Workshop for EPA's Draft Toxicological Review of Halogenated Platinum Salts and Platinum Compounds

Palomar Hotel
2121 P Street, NW
Washington, DC
May 21, 2009

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Appendix B

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Peer Review Workshop for EPA's Draft Toxicological Review of Halogenated Platinum Salts and Platinum Compounds

Palomar Hotel
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Washington, DC
May 21, 2009

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Appendix C

Agenda

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Peer Review Workshop for EPA's Draft Toxicological Review of Halogenated Platinum Salts and Platinum Compounds

Palomar Hotel
2121 P Street, NW
Washington, DC
May 21, 2009

Agenda

8:00 a.m. **Registration**

8:30 a.m. **Welcome, Introductions, Meeting Purpose & Agenda** ..... *Jan Connery, ERG*

8:40 a.m. **EPA Welcome Remarks** .....*Abdel Kadry, IRIS Program Director, EPA NCEA*

8:50 a.m. **Public Comment** .....*Jan Connery*

9:00 a.m. **General Questions** ..... *Rogene Henderson (Chair) & Panel*

G1) **Presentation:** Is the Toxicological Review logical, clear and concise? Has EPA accurately, clearly and objectively represented and synthesized the scientific evidence for noncancer and cancer hazards?
G2) **Additional studies:** Please identify any additional studies that should be considered in the assessment of the noncancer and cancer health effects of halogenated platinum salts and platinum compounds.
G3) **Research:** Please discuss research that you think would be likely to reduce uncertainty in future assessments of halogenated platinum salts and platinum compounds.
G4) **Uncertainty:** Please comment on the identification and characterization of sources of uncertainty in Sections 5 and 6 of the assessment document. Please comment on whether the key sources of uncertainty have been adequately discussed. Have the choices and assumptions made in the discussion of uncertainty been transparently and objectively described? Has the impact of the uncertainty on the assessment been transparently and objectively described?

10:30 a.m. BREAK

10:45 a.m. **Oral RfD for Halogenated Platinum Salts & Compounds** .....*Rogene Henderson & Panel*

A1) **Data to support RfD development:** An RfD was not derived due to lack of adequate data to characterize the health effects associated with oral exposure to halogenated platinum salts and platinum compounds. Are you aware of any data that might support development of an RfD for halogenated platinum salts and platinum compounds?

11:00 a.m. **Inhalation RfC for Halogenated Platinum Salts & Compounds** ....*R. Henderson & Panel*

B1) **Merget et al. (2000) as basis for RfC:** The Merget et al. (2000) occupational epidemiological study was selected as the basis for the RfC. Please provide a detailed explanation of any strengths or weaknesses regarding the Merget et al. (2000) study that are not identified or adequately reviewed in the current assessment. Please comment on whether the selection of this study as the principal study is scientifically justified. Has the rationale for this selection been transparently and objectively described in the document? Please identify and provide the rationale for any other studies that should be selected as the principal study.

B2) **Selection of Pt-specific allergic sensitization as the critical effect:** Pt-specific allergic sensitization, as measured by the development of a positive skin prick test (SPT), was selected as the critical effect for the RfC resulting from exposure to halogenated platinum salts. Please comment on whether the selection of this critical effect is scientifically justified. Is the rationale for this selection transparently and objectively described in the document? Please provide a detailed explanation. Please comment on EPA's rationale regarding adversity of the critical effect. Has it been objectively and transparently described and is it supported by the available data and your understanding of the available scientific data. Please identify and provide the rationales for any other endpoints that should be considered in the selection of the critical effect.

B3) **Derivation of RfC for halogenated Pt salts:** The RfC was quantified for halogenated Pt salts from the Merget et al. (2000) occupational epidemiological study which provided exposure data from airborne soluble Pt measurements that were not further characterized for specific Pt compounds. Please comment on the scientific justification of the derivation of an RfC for halogenated Pt salts from measurements of airborne soluble Pt that were not further characterized for specific Pt compounds. Please identify and provide the rationale for any other approaches that should be considered in the derivation of an RfC for Pt compounds.

Noon LUNCH

1:15 p.m. **Inhalation RfC (cont.)** .....*Rogene Henderson & Panel*

B4) **Statement re use of RfC for Pt compounds other than halogenated Pt salts:** Is the statement that "The use of the RfC for Pt compounds other than halogenated Pt salts is not recommended as the similarity between these compounds and other soluble forms of Pt compounds is unknown" scientifically justified? Please identify and provide the rationale for any other characterization of the platinum compounds that are relevant to the recommended use of the RfC.

B5) **Allergenic activity of Pt/sensitization effects:** EPA has concluded that the allergenic activity of Pt is compound-dependent and sensitization effects appear to be restricted to the halogenated Pt salts. Please comment on whether this finding is justified and supported by the scientific evidence.

B6) **Merget et al. (2000) reporting of SPT positive individuals:** The Merget et al. (2000) study reported 13/115 workers in the high-exposure group developed Pt-specific allergic sensitization (as determined by a positive SPT) during the 5-year study period. The Merget et al. (2000) study did not adjust its reporting of SPT positive individuals for smoking as a risk factor for developing Pt-specific allergic sensitization. Please comment on the potential impact of this approach and implications it may have for the RfC derived from this study.

B7) **Decision not to derive an RfC based on elicitation of an allergic response as the critical effect:** The RfC was derived on the basis that chronic exposure at the dose level would not induce allergic sensitization. However, it is unknown if the RfC would be protective of exacerbation of symptoms in individuals previously sensitized to halogenated platinum salts. Please comment on whether the decision not to derive an RfC based upon elicitation of an allergic response as the critical effect is scientifically sound and has been transparently and objectively described in the document.

B8) **Use of NOAEL approach for determining the POD:** A NOAEL/LOAEL approach was applied to incidence data for Pt-specific allergic sensitization to derive the POD for the RfC. The available data are of marginal adequacy for BMD modeling because only three exposure groups (high, low, and no exposure) are available and only one of these groups has a non-zero response. However, BMD modeling was applied to incidence data for Pt-specific allergic sensitization for comparative purposes. Please provide comments with regard to whether the NOAEL approach is the best approach for determining the POD. Have the NOAEL approach and the BMD modeling approach been appropriately conducted and objectively and transparently described? Please identify and provide rationales for any alternative approaches (including BMR, model, etc.) for the determination of the POD and discuss whether such approaches are preferred to EPA's approach.

B9) **Use of uncertainty factor of 10 to account for interindividual variability:** Insufficient information is available to predict potential variability in susceptibility among the general population to allergic sensitization from inhaled halogenated Pt salts. Please comment on the transparency, scientific rationale and justification for the use of an uncertainty factor of 10 to account for interindividual variability. Are the criteria and rationale for this selection transparently and objectively described in the document? Please comment on whether the justification for selection of this uncertainty factor based on these data is scientifically justified and transparently described.

B10) **Selection of subchronic-to-chronic uncertainty factor of 10:** A subchronic study (Merget et al., 2000) was selected as the principal study with allergic sensitization to halogenated Pt salts as the critical effect for the derivation of the RfC. Please comment on the transparency, scientific rationale and justification for the subchronic to chronic uncertainty factor of 10. Are the criteria and rationale for this selection transparently and objectively described in the document?

B11) **Selection of uncertainty factor of 10 to account for deficiencies in the halogenated platinum salts and platinum compounds database:** An uncertainty factor of 10 was used to account for deficiencies in the halogenated platinum salts and platinum compounds database. The inhalation database currently does not include a chronic, developmental, or a two-generation reproductive toxicity study. Overall, the basic toxicology of halogenated platinum salts and platinum compounds has not been well characterized. Please comment on the transparency, scientific rationale and justification for the selection of the database uncertainty factor. Please comment on whether the application of the database uncertainty factor adequately addresses the lack of toxicity data for halogenated platinum salts and platinum compounds. Are the criteria and rationale for this selection transparently and objectively described in the document?

2:45 p.m. BREAK

3:00 p.m. **Carcinogenicity of Halogenated Platinum Salts & Compounds**.....*R. Henderson & Panel*

C1) **Cancer weight-of-evidence characterization:** Under the EPA's 2005 *Guidelines for Carcinogen Risk Assessment* (www.epa.gov/iris/backgr-d.htm), the Agency concluded that there is *inadequate evidence to determine the carcinogenic potential* of halogenated platinum salts and platinum compounds. Please comment on the cancer weight of evidence characterization. Does the lack of available data support the conclusion that there is *inadequate evidence to determine the carcinogenic potential* of halogenated platinum salts and platinum compounds? Has this recommendation been transparently and objectively described in the document?

3:30 p.m. **Reviewer Final Comments** .....*Rogene Henderson & Panel*

4:00 p.m. **Closing Remarks** ..... *Jan Connery & EPA/NCEA*

4:10 p.m. ADJOURN