Appendix G

Health Effects Information Used In Cancer and Noncancer Risk Characterization for the NATA 1996 National-Scale Assessment

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Introduction

Hazard identification and dose-response assessment information for the NATA national-scale assessment was obtained from various sources and prioritized according to (1) applicability, (2) conceptual consistency with EPA risk assessment guidelines, and (3) level of review received. The prioritization process was aimed at incorporating into our assessment the best-available science with respect to dose-response information. The following sources were used.

US Environmental Protection Agency (EPA)

EPA has developed dose-response assessments for chronic exposure to many of the pollutants in this study. These assessments typically specify a reference concentration, or RfC (to protect against effects other than cancer) and/or a unit risk estimate, or URE (to estimate the probability of contracting cancer). The RfC is an estimate, with uncertainty spanning perhaps an order of magnitude, of an inhalation exposure to the human population (including sensitive subgroups) that is likely to be without appreciable risks of deleterious effects during a lifetime. The URE is the upper-bound excess cancer risk estimated to result from a lifetime of continuous exposure to an agent at a concentration of 1 $\mu g/m^3$ in air. In assessing a substance's carcinogenic potential, EPA evaluates various types of toxicological data and develops a weight-of-evidence (WOE) determination. Current WOE assessments include an alphanumeric categorization (as per EPA's 1986 guidelines for carcinogen risk assessment) and a paragraph of descriptive text (as per the current draft revisions to these guidelines).

EPA disseminates dose-response assessment information in several forms, depending on the level of internal review. EPA publishes dose-response assessments that have achieved full intra-agency consensus on its Integrated Risk Information System (IRIS), which is regularly updated (EPA, available on-line at www.epa.gov/iris). Many IRIS assessments have also undergone external scientific peer review.

Agency for Toxic Substances and Disease Registry (ATSDR)

ATSDR, which is part of the US Department of Health and Human Services, develops and publishes Minimal Risk Levels (MRLs) for many toxic substances. The MRL is defined as an estimate of daily human exposure to a substance that is likely to be without an appreciable risk of adverse effects (other than cancer) over a specified duration of exposure. MRLs can be derived for acute, intermediate, and chronic duration exposures by the inhalation and oral routes. ATSDR describes MRLs as media-specific concentrations to be used by health assessors to select environmental contaminants for further evaluation. They are presented with only 1 significant figure, and are considered concentrations below which contaminants are unlikely to pose a health threat. Concentrations above an MRL do not necessarily represent a threat, and MRLs are therefore not intended for use as predictors of adverse health effects or for setting cleanup levels.

Inhalation MRLs were used in the noncancer portion of this assessment when IRIS RfCs were not available because their concept, definition, and derivation are philosophically consistent (though not identical) with the basis for EPA's RfC. ATSDR publishes MRLs as part of pollutant-specific toxicological profile documents. MRLs are also collected in a table of "comparison values", regularly updated and distributed by ATSDR.

California Environmental Protection Agency (CalEPA)

The CalEPA Air Resources Board has developed dose-response assessments for many HAPs, based both on carcinogenicity and health effects other than cancer. The process for developing these assessments is similar to that used by the EPA to develop IRIS values and incorporates significant external scientific peer review. The non-cancer information includes available inhalation health risk guidance values expressed as chronic inhalation reference exposure levels (RELs). CalEPA defines the REL as a concentration level at (or below) which no health effects are anticipated, a concept that is substantially similar to EPA's non-cancer dose-response assessment perspective. This assessment uses chronic RELs in the same way as RfCs when no IRIS or ATSDR values exist.

CalEPA's quantitative dose-response information on carcinogenicity by inhalation exposure is expressed in terms of the URE, defined similarly to EPA's URE. This assessment uses specific CalEPA UREs in the same way as EPA's when no IRIS or values exist.

International Agency for Research on Cancer (IARC)

The IARC, a branch of the World Health Organization, coordinates and conducts research on the causes of human cancer and develops scientific strategies for cancer control. The IARC sponsors both epidemiological and laboratory research, and disseminates scientific information through meetings, publications, courses and fellowships.

As part of its mission, the IARC assembles evidence that substances cause cancer in humans and issues judgments on the strength of evidence. IARC's "degrees of evidence" categories are Group 1 (carcinogenic in humans), Group 2A (probably carcinogenic), Group 2B (possibly carcinogenic), Group 3 (not classifiable), and Group 4 (probably not carcinogenic). The categorization scheme may be applied to either single chemicals or mixtures. The IARC does not develop quantitative dose-response indices such as UREs, however.

IARC's WOE for HAPs are included as supporting information for this assessment as a backup to EPA's WOE determinations, which do not cover all HAPs and in some cases may be out-of-date.

Prioritization of Data Sources

Some HAPs have been subjected to dose-response assessments by several of the agencies used as sources for this analysis. Because different scientists developed these assessments at different times for purposes that were similar but not identical, it is inevitable that the results are not totally consistent. To resolve inter-agency discrepancies for this analysis, EPA applied a consistent priority scheme to the universe of dose-response information.

RfCs and UREs for chronic inhalation exposure obtained from EPA's IRIS database (or from advanced drafts of IRIS assessments) were given first priority. For HAPs lacking IRIS data, ATSDR MRLs (available only for noncancer effects) received next preference, followed in order by CalEPA RELs and UREs and other cancer and noncancer assessments published in EPA's HEAST. Further information on the development of dose-response assessments by these agencies is available on-line at www.epa.gov/iris, www.atsdr1.atsdr.cdc.gov:8080/mrls.html, www.oehha.ca.gov/air/hot_spots/index.html, and http://193.51.164.11/monoeval/grlist.html.

For two carcinogenic HAPs, quinoline and 1,2-dichloropropane, that currently lack inhalation assessments from these sources, IRIS oral carcinogenic potency estimates were converted to inhalation UREs. (Oral-to-inhalation conversion was not done for non-cancer effects.) EPA understands that conversion of oral dose-response information to inhalation exposure is a problematic risk assessment practice. However, the alternative to this would have been to omit such HAPs from quantitative risk estimates altogether, thereby making a *de facto* assumption of zero carcinogenic potency. EPA regards this alternative as unacceptable for the purposes of this national-scale assessment.

Assumptions on Speciation and Other Adjustments to Dose-Response Information

Following the prioritization of dose-response information, the following EPA made the following adjustments based on professional judgment:

1. 1,3-Butadiene. In April 1999, the EPA Office of Research and Development (ORD) informed the Office of Air Quality Planning and Standards (OAQPS) that the URE for 1,3-butadiene currently on IRIS (2.8e-4 per $\mu g/m^3$) was no longer supportable. The memo recommended an interim URE (2.08e-6 per $\mu g/m^3$) that was more than two orders of magnitude lower (*i.e.*, less potent). OAQPS has since received a followup recommendation from ORD recommending 4.0E-06 per $\mu g/m^3$ as the best interim URE. In accordance with ORD's most recent recommendation, this assessment used 4.0E-06 as the URE for 1,3-butadiene.

2. Chromium. For chromium compounds, the IRIS RfC for particulate hexavalent chromium was used in preference to the RfC for chromic acid mists and dissolved aerosols. Both the RfC and the URE for hexavalent chromium were adjusted to reflect an assumption that 34% of all atmospheric chromium is hexavalent. This represents the best judgment of EPA staff, based on limited data on species of chromium emitted from five significant source categories. The total chromium mass in these emissions ranged from 0.4% to 70% hexavalent. Because the high end of the range was associated exclusively with electroplating sources, EPA chose 34%, the upper end of the range for utility boilers. It is likely that most sources of chromium emissions in the US contain smaller amounts of hexavalent chromium.

3. Lead. For lead and compounds, the CalEPA URE was used for carcinogenic effects. For effects other than cancer, the EPA national ambient air quality standard was used as an RfC equivalent.

4. Nickel. The IRIS unit risk for nickel inhalation was derived from evidence of the carcinogenic effects of insoluble nickel compounds in crystalline form. Soluble nickel species, and insoluble

species in amorphous form, do not appear to produce genotoxic effects by the same toxic mode of action as insoluble crystalline nickel. Nickel speciation information for some of the largest nickel-emitting sources (including oil combustion, coal combustion, and others) suggests that at least 35% of total nickel emissions may be soluble compounds. The remaining insoluble nickel emissions are not well-characterized, however. Consistent with this limited information, this analysis has conservatively assumed that 65% of emitted nickel is insoluble, and that all insoluble nickel is crystalline. On this basis, the URE for nickel subsulfide (representing pure insoluble crystalline nickel) was multiplied by 0.65 and applied to all nickel compounds.

5. Polycyclic Organic Matter. The assessment considered polycyclic organic matter (POM) in two ways. First, it focused on a subgroup of seven carcinogenic polynuclear aromatic hydrocarbon (PAH) compounds (i.e., benz[a]anthracene, benzo[b]fluoranthene, benzo[k]fluoranthene, benzo[a]pyrene, chrysene, dibenz[a,h]anthracene, and indeno[1,2,3-cd]pyrene) within the POM category. Because these compounds were tracked as a group in the 1996 NTI, their emissions were more completely characterized than those of the rest of the POM category. The "7-PAH" compounds as a group were assumed to have a carcinogenic potency equal to 18% of that for pure benzo[a]pyrene. Second, the assessment considered POM emissions reported in the 1996 NTI as "total POM." Total POM reported as a group were assumed to have a carcinogenic potency equal to 5% of that for pure benzo[a]pyrene. Details of the derivation of these relative potency estimates are presented in Appendix H.

Table of Cancer Dose-Response Values

The process of URE estimation includes several important sources of uncertainty. First, many of the HAPs in this assessment were classified as probable carcinogens, which means that data were not sufficient to prove these substances definitely cause cancer in humans. It is possible that some are not human carcinogens at environmentally relevant doses, and that the true risk associated with these HAPs is zero. Second, all UREs used in this assessment were based on linear extrapolation from high to low doses. To the extent that true dose-response relationships for some HAPs are nonlinear, this assumption may result in significant over- or underestimates of risk. Third, UREs for most of these substances were developed from animal data using conservative methods to extrapolate between species. Actual human responses may differ from the predicted ones. Fourth, most UREs used in this assessment (typically, those based on animal data) were based on the statistical upper confidence limit (UCL) of the fitted dose-response curve, but a few (typically, those based on human data) were based on the statistical best fit ("maximum likelihood estimate," or MLE). The reader should be aware that URE estimates for some known carcinogens are somewhat less conservative than most UREs. Nevertheless, because of the combination of assumptions used in the face of all four sources of uncertainty described above, EPA considers all its UREs to be upper-bound estimates. True risk would probably be less, but could be greater.

The following table lists the HAPs for which quantitative cancer risk estimates have been developed for the initial 1996 national-scale assessment. The EPA and IARC weight-of-evidence (WOE) characterizes the extent to which the available data support the hypothesis that a pollutant causes cancer in humans. The EPA categories are Group A—known, Group B1—probable, based on incomplete human data, Group B2—probable, based on adequate animal data, Group C—possible, Group D—not classifiable, and Group E—evidence of non-carcinogenicity. The IARC categories are Group 1—carcinogenic in humans, Group 2A—probably carcinogenic, Group 2B—possibly

carcinogenic, Group 3—not classifiable, and Group 4—probably not carcinogenic. The URE is the upper bound risk estimate of cancer risk from a lifetime exposure to a concentration of 1 microgram per cubic meter. The source column contains the origin of the URE. "CONV ORAL" in the source column denotes UREs developed by converting oral potency values, done for substances for which UREs were not otherwise available. IRIS assessments that conform to both the 1986 cancer guidelines and the newly proposed revised guidelines are shown with a '4' superscript. The IRIS assessment for one HAP, benzene, recommended a URE range; the value in the table is the upper end of that range.

Urban HAP	Weight of Evidence		Unit Risk (per ug/m^3)	Source
	EPA	IARC		
Acetaldehyde	B2	2B	2.2E-06	IRIS[1]
Acrylonitrile	B1	2A	6.8E-05	IRIS[1]
Arsenic compounds	A	1	4.3E-03	IRIS[2]
Benzene	A	1	7.8E-06	IRIS[2,3,4]
Beryllium compounds	B1	1	2.4E-03	IRIS[1,4]
1,3-Butadiene	B2	2A	1E-05	EPA NCEA [1,4,5]
Cadmium compounds	B1	1	1.8E-03	IRIS[1]
Carbon tetrachloride	B2	2B	1.5E-05	IRIS[1]
Chloroform	B2	2B	2.3E-05	IRIS[1]
Chromium compounds	A	1	4.1E-03	IRIS[2,4,6]
Coke Oven Emissions	A	-	6.2E-04	IRIS[1]
1,3-Dichloropropene	B2	2B	4.0E-06	IRIS[1,4]
Ethylene dibromide (1,2-dibromoethane)	B2	2A	2.2E-04	IRIS[1]
Ethylene dichloride (1,2-dichloroethane)	B2	2B	2.6E-05	IRIS[1]
Ethylene oxide	B1	1	8.8E-05	CAL EPA
Formaldehyde	B1	2A	1.3E-05	IRIS[1]
Hexachlorobenzene	B2	2B	4.6E-04	IRIS[1]
Hydrazine, hydrazine sulfate	B2	2B	4.9E-03	IRIS[1]
Lead compounds	B2	2B	1.2E-05	CAL EPA
Methylene chloride	B2	2B	4.7E-07	IRIS[1]
Nickel compounds	A	2B	1.2E-04	IRIS[1,6]
Polychlorinated biphenyls (PCBs)	B2	2A	1.1E-04	IRIS[1]

[1] Upper confidence limit URE; (assessments that did not specify method were assumed to use the UCL).
[2] Maximum likelihood URE.
[3] Higher of 2 recommended UREs was selected.
[4] Assessment consistent with 1996 proposed cancer guidelines.
[5] Advanced draft of IRIS assessment, expected to be finalized shortly.
[6] Value includes assumptions on speciation of emissions; details provided in text above.

Urban HAP	Weight of Evidence		Unit Risk (per ug/m^3)	Source
	EPA	IARC		
Polycyclic Organic Matter	[7]	[7]	5.5E-05	[8]
Carcinogenic PAHs: 7-PAH	B2	[7]	2.0E-04	[8]
Propylene dichloride (1,2-dichloropropane)	B2	3	1.9E-05	CONV ORAL[1]
Quinoline	C	-	3.4E-03	CONV ORAL[1]
1,1,2,2-Tetrachloroethane	C	3	5.8E-05	IRIS[1]
Tetrachloroethylene (perchloroethylene)	B2-C	2A	5.9E-06	CAL EPA
Trichloroethylene (TCE)	B2-C	2A	2.0E-06	CAL EPA
Vinyl chloride	A	1	8.8E-06	IRIS[1,4,9]

Table of Non-Cancer Dose-Response Values

The following table lists HAPs for which quantitative estimates of non-cancer hazard have been developed for the initial 1996 national-scale assessment. The reference concentration (RfC) is an estimate, with uncertainty spanning perhaps an order of magnitude, of an inhalation exposure to the human population (including sensitive subgroups) that is likely to be without appreciable risks of deleterious effects during a lifetime. Where EPA RfCs are absent, similar values developed by other agencies have been used. The UF and MF are the uncertainty factor and modifying factor used in the development of the RfC. In general, experimental doses are adjusted by these factors to derive dose levels that should be generally without adverse effect. The target organ for critical effects is the organ or organ system adversely affected at the lowest dose in human or animal studies. The target organs for other effects are those organs or systems adversely affected at higher doses.

Urban HAP	CAS #	RfC (or Equivalent)[10] (mg/m3)	UFxMF[11]	Target Organ for Chronic Critical Effect[12]	Target Organs for Other Chronic Effects	Source
Acetaldehyde	75070	9.0E-03	1000	Nasal epithelium	Growth rate, blood, and kidney	IRIS
Acrolein	107028	2.0E-05	1000	Nasal epithelium	Mucous membranes (irritation)	IRIS
Acrylonitrile	107131	2.0E-03	100/10	Nasal epithelium, brain	Central nervous system	IRIS

[7] WOE varies among individual compounds.
[8] The CalEPA estimates for various polycyclic organic compounds are based on a toxic equivalency approach, where the potency of individual compounds is estimated based on relative activity rather than individual assessments of bioassay data. The development of UREs for total POM and 7-PAH is described in Appendix H.
[9] URE based on whole life exposure was selected over a URE based on adult exposure only.
[10] Includes EPA reference concentrations (RfCs), Cal EPA reference exposure levels (RELs), ATSDR minimum risk levels (MRLs), and HEAST inhalation reference doses (RfDs) converted to concentrations in air.
[11] Modifying factors of 1 are not shown.
[12] Critical effect listed is the adverse effect upon which the RfC or equivalent health-based value is based.

Urban HAP	CAS #	RfC (or Equivalent)[10] (mg/m3)	UFxMF[11]	Target Organ for Chronic Critical Effect[12]	Target Organs for Other Chronic Effects	Source
					(depression)	
Arsenic compounds	AS_CMPDS	3.0E-05	1000	Skeleton (fetal malformation)	Skin and mucous membranes (irritation)	CAL EPA
Benzene	71432	6.0E-02	10	Blood, bone marrow	Central nervous system (depression)	CAL EPA
Beryllium compounds	BE_CMPDS	2.0E-05	10	Lung	Immune system	IRIS
1,3-Butadiene	106990	8.0E-03	300	Reproductive system	Cardiovascular system, blood	CAL EPA
Cadmium compounds	CD_CMPDS	2.0E-05	30	Kidney	Lung	CAL EPA
Carbon tetrachloride	56235	4.0E-02	300	Liver	Kidney	CAL EPA
Chloroform	67663	9.8E-02	100	Liver, kidney	Central nervous system (depression)	ATSDR
Chromium compounds	CR_CMPDS	1.0E-04	90	Respiratory tract (necrosis)	Liver, kidney, GI tract, immune system	IRIS
1,3-Dichloropropene	542756	2.0E-02	30	Nasal epithelium	Urinary bladder	IRIS
Ethylene dibromide (1,2-dibromoethane)	106934	8.0E-04	100	Reproductive system	Liver, kidney, testes	CAL EPA
Ethylene dichloride (1,2-dichloroethane)	107062	2.4E+00	90	Kidney	Liver	ATSDR
Ethylene oxide	75218	3.0E-02	100	Blood	Eyes, mucous membranes, central nervous system	CAL EPA
Formaldehyde	50000	9.8E-03	30	Respiratory epithelium	Immune system (sensitization)	ATSDR
Hexachlorobenzene	118741	3.0E-03	100	Liver (developmental)	Immune system, kidney, blood	CAL EPA
Hydrazine, hydrazine sulfate	302012	2.0E-04	300	Liver, thyroid	Respiratory system, spleen	CAL EPA
Lead compounds[13]	PB_CMPDS	1.5E-03	1	Central nervous system (neurobehavioral effects)	Blood, cardiovascular system, kidney	NAAQS
Manganese compounds	MN_CMPDS	5.0E-05	1000	Central nervous system (neurobehavioral effects)	Respiratory system	IRIS
Mercury compounds[14]	HG_CMPDS	3.0E-04	30	Central nervous system	-	IRIS
Methylene chloride	75092	1.0E+00	30	Liver	Kidney, cardiovascular	ATSDR

[13] EPA has not developed an RfC for lead. The NSA uses the National Ambient Air Quality Standard for lead, which was developed using the EPA Integrated Exposure, Uptake, Biokinetic Model, and did not use the UF/MF method. Because sensitive human subpopulations were modeled, the effective UF is 1.

[14] Hazard calculations for mercury compounds were based on the RfC for elemental mercury.

Urban HAP	CAS #	RfC (or Equivalent)[10] (mg/m3)	UFxMF[11]	Target Organ for Chronic Critical Effect[12]	Target Organs for Other Chronic Effects	Source
					system	
Nickel compounds	NI_CMPDS	2.0E-04	30	Respiratory system, immune system	-	ATSDR
Propylene dichloride (1,2-dichloropropane)	78875	4.0E-03	300	Nasal epithelium	Blood	IRIS
Tetrachloroethylene (perchloroethylene)	127184	2.7E-01	100	Central nervous system (depression)	Heart, liver, kidney	ATSDR
Trichloroethylene (TCE)	79016	6.0E-01	100	Central nervous system (depression)	Liver, kidney	CAL EPA
Vinyl chloride	75014	1.0E-01	300	Liver	Kidney, central nervous system (depression)	IRIS