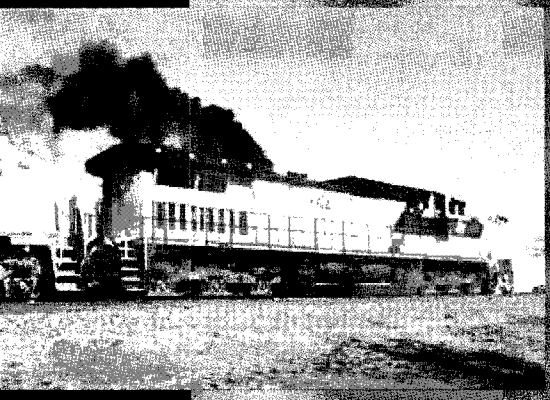
Diesel and Health in America: The Lingering Threat

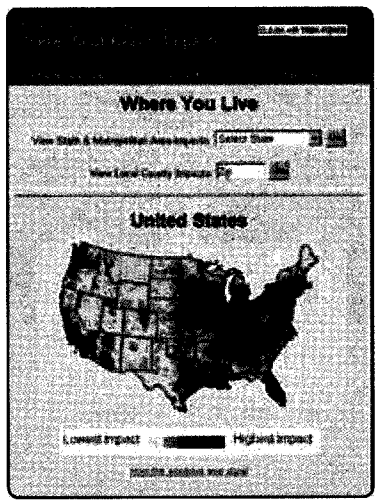


CLEAN AIR TASK FORCE

February 2005

Find out about the risks
of breathing diesel exhaust
where you live:

www.catf.us/goto/dieselhealth



CLEAN AIR **TASK FORCE**

18 Tremont Street, Suite 530, Boston, MA 02108
Tel: 617-624-0234 / Fax: 617-624-0230

Credits –

Written by: **Conrad G. Schneider**, *Advocacy Director*
and **L. Bruce Hill, Ph.D.**, *Senior Scientist*

Edited by: **Maria Padian**

Designed by: **Jill Bock Design**

Printed by: **Spectrum Printing & Graphics, Inc.**

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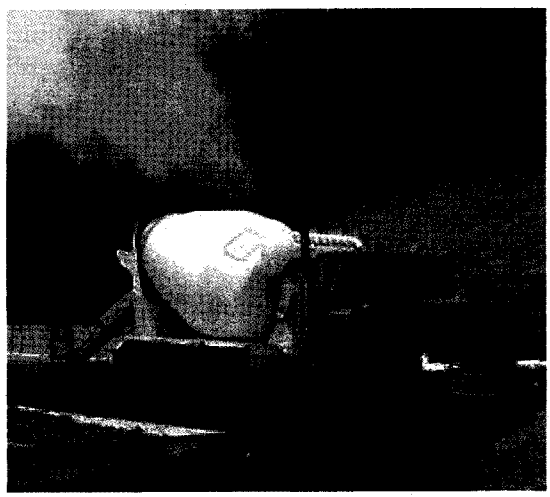
February 2005

Foreword

Scientists have been examining relationships between air pollution and death and disease for decades but only now are we beginning to understand the impacts of one of the most toxic sources of emissions today – the diesel engine. Diesels churn out a hazardous mix of gaseous and particle pollutants. What's more, diesel exhaust is emitted at ground level – where we breathe it – by trucks and buses around us in traffic, at school and transit bus stops, and by heavy construction or agricultural equipment. Diesel exhaust contains numerous dangerous compounds, ranging from respiratory irritants to carcinogens including a host of air toxics, particulate matter, carbon monoxide and nitrogen oxides.



While scientists have concluded that combustion-related particulate matter from all combustion sources is associated with premature death from heart attacks and cancer, we also are finding that carbon particles from mobile sources may be particularly unhealthy. These particles adsorb other metals and toxic gases produced by diesel engines – such as cancer causing-PAH (polycyclic aromatic hydrocarbons) – onto their surfaces making them even more dangerous. Furthermore, research on personal exposures demonstrates that these small particles easily penetrate our indoor environment where they may be trapped for days when ventilation is poor.

This report presents for the first time estimates of the health toll from diesel vehicle pollution. Using methodology approved by the U.S. Environmental Protection Agency's Science Advisory Board (SAB), the analysis finds that approximately 21,000 people die prematurely each year due to particulate matter pollution from diesels. Other serious adverse health impacts include tens of thousands of heart attacks, asthma attacks, and other respiratory ailments that can lead to days missed at work and at school.

Using more highly time-resolved studies we are increasingly able to understand the inflammation mechanism by which particles can lead to atherosclerosis, heart attacks, strokes and ultimately, untimely deaths. From all we know today, we can confidently say that reducing diesel exhaust in our environment will mean improving public health, and as this report demonstrates, reducing preventable premature deaths. We do not need to wait. Technology is available today that can reduce particulate matter emissions by up to 90 percent. Now is the time to clean up our old trucks, buses, heavy equipment and locomotives to provide a cleaner future for us and our children.

Howard Frumkin, M.D., Dr.P.H., FACP, FACOEM
Professor and Chair, Department of Environmental and Occupational Health
Emory University, Rollins School of Public Health

Executive Summary

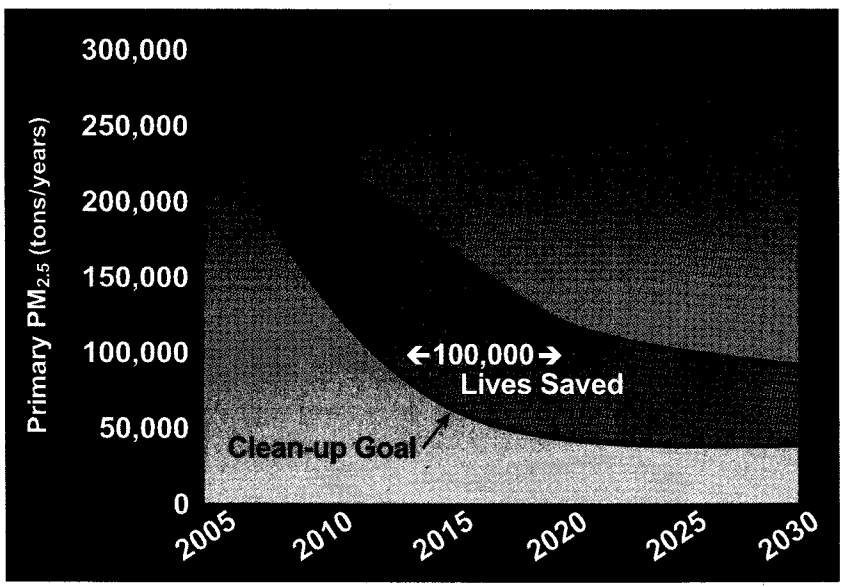
Everyone has experienced it: getting hit right in the face by a cloud of acrid diesel smoke. Perhaps you were standing on a street corner when a bus or truck whizzed by. Or maybe you were standing at a bus stop or stuck behind a dump truck grinding up a hill. But breathing diesel exhaust isn't just unpleasant. It is hazardous to your health. In fact, health research indicates that the portion of the exhaust you can't see may be the most dangerous of all. Asthma attacks, respiratory disease, heart attacks, and even premature death – all of these are among the most serious public health problems linked to emissions from the nation's fleet of diesel vehicles. The good news is that the technology exists right now to clean up emissions from these engines, so that most of the adverse health impacts can be prevented.

Today in the U.S. more than 13 million diesel vehicles help to build our cities and towns, transport our food and goods, and take us to and from work. More than three quarters of all Americans live near intersections, bus stops, highways, bus and truck depots, or construction sites with heavy equipment – all of which are concentrated sources of diesel exhaust. In rural areas, those who live near heavy diesel agricultural equipment suffer their share of exposure to diesel as well.

The U.S. Environmental Protection Agency has issued important regulations that will require dramatic reductions in emissions from new diesel vehicles starting in 2007 – but only the new ones. These regulations, to be phased in over the next quarter century, apply only to ***new*** engines. What about the diesels on the road today? The lifespan of the

average diesel vehicle is nearly 30 years. Many diesels are driven over a million miles. Because of this longevity, we will be left with the legacy of pollution from dirty diesel vehicles for decades to come. That is, ***unless*** we take action to reduce emissions from vehicles currently on the road. We don't have to wait. Control technologies exist right now that can significantly reduce deadly fine particle emissions from diesel vehicles, in some cases by upwards of 90 percent.

American know-how, witnessed by the success of the manufacturers of engines, control devices, and fuel refiners in developing innovative solutions for reducing diesel exhaust, provides a lifesaving opportunity we can seize today. Pollution from dirty diesels on the road now can be dramatically reduced using a combination of cleaner fuels, retrofit emission controls, rebuilt engines, engine repowerings, and accelerated purchase of new, cleaner vehicles. Unlike so many other vexing environmental issues, these affordable solutions present a highly unusual opportunity to actually address a major risk to public health and the environment. In fact, we could virtually eliminate this problem if diesel manufacturers, fleet owners, environmentalists, concerned citizens, and government regulators make the commitment to work together.



An Aggressive Program to Reduce Diesel Emissions Could Save About 100,000 Lives between Now and the Year 2030.

What are the health impacts of these dirty diesel vehicles? What benefits will we realize if we act now to clean them up? The Clean Air Task Force commissioned Abt Associates, an highly-respected consulting firm that U.S. EPA and other agencies rely upon to assess the benefits of national air quality policies, to quantify for the first time the health impacts of fine particle air pollution from America's diesel fleet. Using this information, we were able to estimate the expected benefits – in lives saved – from an aggressive but feasible program to clean up dirty diesel buses, trucks, and heavy equipment across the U.S.

This report summarizes the findings of the Abt Associates study. It then reviews the degree to which diesel vehicles increase the level of fine particle pollution in the air we breathe, and recommends reduction measures that will save thousands of lives each year.

Key findings include:

- Reducing diesel fine particle emissions 50 percent by 2010, 75 percent by 2015, and 85 percent by 2020 would save nearly 100,000 lives between now and 2030. These are additional lives saved above and beyond the projected impact of EPA's new engine regulations.
- Fine particle pollution from diesels shortens the lives of nearly 21,000 people each year. This includes almost 3,000 early deaths from lung cancer.
- Tens of thousands of Americans suffer each year from asthma attacks (over 400,000), heart attacks (27,000), and respiratory problems associated with fine particles from diesel vehicles. These illnesses result in thousands of emergency room visits, hospitalizations, and lost work days. Together with the toll of premature deaths, the health damages from diesel fine particles will total $139 billion in 2010.
- Nationally, diesel exhaust poses a cancer risk that is 7.5 times higher than the ***combined*** total cancer risk from all other air toxics.
- In the U.S., the average lifetime nationwide cancer risk due to diesel exhaust is over 350 times greater than the level U.S. EPA considers to be "acceptable" (i.e., one cancer per million persons over 70 years).
- Residents from more than two-thirds of all U.S. counties face a cancer risk from diesel exhaust greater than 100 deaths per million population. People living in eleven urban counties face diesel cancer risks greater than 1,000 in a million – one thousand times the level EPA says is acceptable.
- People who live in metropolitan areas with a high concentration of diesel vehicles and traffic feel their impacts most acutely. The risk of lung cancer from diesel exhaust for people living in urban areas is three times that for those living in rural areas.

The vast majority of the deaths due to dirty diesels could be avoided by an aggressive program over the next 15 years to require cleanup of the nation's existing diesel fleet. Practical, affordable solutions are available that can achieve substantial reductions in diesel risk. The only thing that stands between us and dramatically healthier air is the political will to require these reductions and the funding to make it a reality.

What We Must Do to Protect Public Health from Today's Dirty Diesels.

Although the EPA has mandated the phase-in of cleaner new engines and fuels beginning in 2007 for highway vehicles and heavy equipment, EPA has limited authority to mandate emissions controls on the fleet of existing diesel vehicles. To date, EPA has adopted a "voluntary" approach. Nevertheless, in order to meet the new ambient air quality standards for fine particles, states and cities must require controls to reduce diesel emissions. Diesel cleanup is also an important next step in areas that are having difficulty meeting existing and new ambient air quality standards for ozone such as Houston and Dallas, Texas.

States can enact legislation requiring diesel cleanup as some, such as California and Texas, have already begun to do. States should also consider measures to require early engine retirement and speed fleet turnover. For vehicles like long-haul trucks, ships, and locomotives that are engaged in interstate transport, federal regulations, federal legislation, or both may be needed. Funding for such initiatives may pose a challenge for public fleets (school buses, transit vehicles, garbage trucks, etc.), so support for expanded state and federal funding to help the cleanup of fleets owned by cash-strapped states and cities will be necessary. Local and state budget writers will need a strong commitment to come up with the necessary appropriations or bonds to fund the local share.

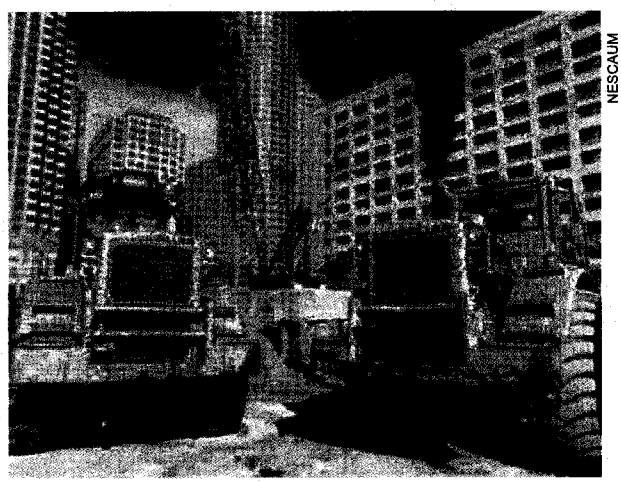
Particle filters combined with the use of Ultra Low Sulfur Diesel (ULSD) fuel have been found to reduce diesel particles and particle-bound toxics from diesel exhaust by up to 90 percent. Under the new engine rules, ULSD will be available for highway vehicles nationwide starting in 2006. It is already available in cities in 21 states. Not all vehicles can be retrofitted with a particle filter, but there are a variety of options available for the cleanup of every vehicle regardless of make or model year.

Cities and states should:

- Establish ambitious goals for reducing risk to their citizens by cleaning up existing diesels;
- Identify priority geographic areas and diesel "hotspots" for immediate attention;
- Adopt a package of options for reducing diesel exhaust including:
  - Retrofits accomplished by replacing mufflers with an optimal mix of filters or oxidation catalysts depending on vehicle age and type;
  - Requiring Ultra Low Sulfur Diesel and cleaner alternative fuels;
  - Closed crankcase ventilation systems to eliminate engine exhaust from penetrating the cabin of vehicles such as school and transit buses;
  - Engine rebuild and replacement requirements;
  - Truck stop electrification programs to give long-haul truckers a way to power their rigs overnight without running their engines;
  - Contract specifications requiring cleanup of trucks and construction equipment used in public works projects.
- Adopt diesel cleanup measures as federally-enforceable requirements in State Implementation Plans (SIPs) for the attainment of the fine particle and ozone air quality standards;
- Create and fund programs, such as California's "Carl Moyer" and the Texas Emission Reduction Plan (TERP) program, which provide funding for diesel equipment owners to replace or rebuild high-polluting diesel engines;
- Adopt and enforce anti-idling ordinances and legislation.

The Federal government should:

- Pass legislation providing funding for the cleanup of municipal and state fleet vehicles;
- Explore regulatory options for reducing emissions from existing interstate fleets such as long-haul trucks, shipping, and locomotives;
- Retain and enforce the tighter new engine and cleaner fuel standards for highway and non-road diesels.



NESCAUM

Retrofits are effective in reducing particle emissions from heavy equipment. The tractor on the left is retrofitted with a particle emissions control device.

New Findings

While numerous medical studies have linked diesel exhaust to a host of serious adverse health outcomes, no single study has yet quantified the death and disease attributable to diesel across America – until now. Researchers estimate that as many as 60,000 people in the U.S. die prematurely each year because of exposure to fine particles from all sources.[1] And some researchers believe that this figure may even underestimate the total number of particle-related deaths.[2] A reanalysis of the major particle mortality study in over 150 cities suggests that particles from motor vehicles may be more toxic than average.[3]

We know that diesel exhaust is a hazardous mixture of gases and particles including carcinogens, mutagens, respiratory irritants or inflammatory agents and other toxins that cause a range of diverse health effects. Diesel particles act like magnets for toxic organic chemicals and metals. The smallest of these particles (ultrafine particles) can penetrate deep into the lung and enter the bloodstream, carrying with them an array of toxins.[4] Diesel exhaust can contain 40 hazardous air pollutants as listed by EPA, 15 of which are listed by the International Agency for Research on cancer (IARC) as known, probable or possible human carcinogens.[5] Thousands of studies also have documented that fine particles are associated with respiratory and cardiovascular diseases and death. Additional studies have documented effects in infants and children such as Sudden Infant Death syndrome (SIDS) and retarded lung development.[6]

Now, for the first time, this report reveals the staggering toll of death and disease from diesel exhaust in our air – and the dramatic benefits of requiring the cleanup of the nation's existing diesel fleet. Abt Associates, using peer-reviewed, state-of-the-art research methodology employed by U.S. EPA in assessing the national benefits of proposed

National Annual Diesel Fine Particle Health Impacts[7]

Annual Cases in the U.S., 2010	
Premature Deaths	21,000
Lung Cancer Deaths	3,000
Hospital Admissions	15,000
Emergency Room Visits for Asthma	15,000
Non-fatal Heart Attacks	27,000
Asthma Attacks	410,000
Chronic Bronchitis	12,000
Work Loss Days	2,400,000
Restricted Activity Days	14,000,000

rules and legislation, finds that nearly 21,000 people will die prematurely in 2010 in the U.S. as a result of exposure to fine particle emissions from mobile diesel sources (i.e., all on-and non-road engines such as highway, construction, rail, and marine engines). The average number of life-years lost by those who die prematurely from exposure to fine particles is 14 years.[8]

The deaths from diesel fine particle pollution equal or exceed the death toll from other causes commonly understood to be major public policy priorities. For instance, drunk driving causes more than 17,000 deaths per year.[9] There are more than 20,000 homicides in the U.S. each year.[10] Moreover, the approximately 15,000 premature deaths per year that could be avoided by achieving a 75 percent diesel-risk-reduction target exceed the 11,000 automobile fatalities avoided each year through the use of safety belts.[11]

The Abt Associates analysis further shows that hundreds of thousands of Americans suffer from asthma attacks, cardiac problems, and respiratory ailments associated with fine particles from diesels. These health damages result in thousands of respiratory and cardio-pulmonary related hospitalizations and emergency room visits annually as well as hundreds of thousands of lost work days each year. For instance, the study finds that diesel pollution leads to 27,000 heart attacks and 400,000 asthma attacks each year.[12]

You can find the adverse health impacts from diesel for your state, metropolitan area, and county on the web at: **www.catf.us/goto/dieselhealth**.

The risk from diesel exhaust can be virtually eliminated by the application of emissions control strategies available today. For example, an aggressive but feasible program to reduce diesel particle emissions nationwide 50 percent by 2010, 75 percent by 2015, and 85 percent by 2020 would save about 100,000 lives between now and 2030 – beyond those lives that will be saved under EPA's new engine regulations.[13] Indeed, in the year 2000, the State of California set a Diesel Risk Reduction goal of a 75 percent reduction in diesel risk by 2010 and 85 percent by 2020 and the California Air Resources Board over the past few years has begun to issue regulations to achieve it.[14]

Cancer Risk

CATF has calculated the national average lifetime excess cancer risk posed by diesel. We base these estimates on 1999 modeled directly-emitted diesel fine particle concentrations and by applying both the EPA range of individual risk estimates and the California Air Resources Board (CARB) diesel risk factor for lung cancer over the U.S. population.[15] Although EPA has found diesel exhaust to be a "likely" human carcinogen, EPA has not adopted a risk factor but has, instead, provided a range of lung cancer risk.[16] Based on the national average diesel particulate matter concentration, we find average lung cancer risk ranges from 12 to 1210 per million people over a 70-year lifetime using EPA's range of lung cancer risk.[17] Using the same methodology, CATF finds that, based on the single CARB risk factor, the nationwide average lifetime cancer risk posed by diesel exhaust is over 350 times greater than EPA's "acceptable" level of one cancer in a million.

For comparison, according to EPA's 1999 NATA assessment, the combined risk from all other air toxics is 48 per million.[18] Therefore, diesel exhaust presents a lung cancer risk that is 7.5 times higher than the cancer risk of all other air toxics – ***combined!***[19] In addition, CATF has calculated the cancer risk posed by diesel for residents of each U.S. county. Residents of over two-thirds of U.S. counties experience a cancer risk greater than 100 in a million from diesel exhaust. Moreover, residents of eleven urban U.S. counties face a diesel cancer risk equal to 1,000 new cases of cancer in a population of one million.

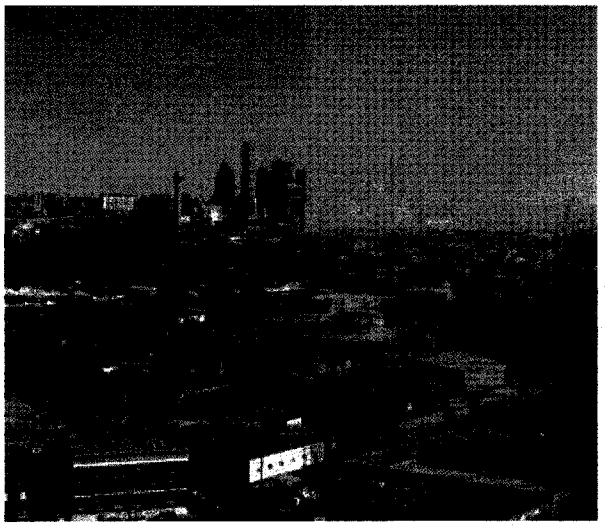
People who live in metropolitan areas with a high concentration of diesel vehicles and traffic feel their impacts

most acutely. For example, the estimated risk of lung cancer from diesel in metropolitan areas is much higher than in areas with fewer diesels. In the rural counties we estimate a risk of 142 cancers per million based on the CARB unit risk, but three times that rate, 415 cancer per million, in urban counties. Therefore, the risk of lung cancer for people living in urban areas is three times that for those living in rural areas.[20]

You can find the community cancer risk from diesel for your state, metropolitan area, and county on the web at: **www.catf.us/goto/dieselhealth**. Personal risk varies with location and lifestyle. For example, if you live near a bus, truck, or train terminal, highway, construction site, or warehouse, or commute to work on congested roadways, your exposure may be higher than indicated by the county-wide average estimated here.

The Economic Toll of Health Effects

Respiratory distress severe enough to require a trip to the emergency room can be a terrifying experience for patients and their families. Victims of asthma attacks say that during an attack they wonder if and when their next breath will come. In addition to its serious physical and emotional costs, air pollution also takes a large monetary toll. Emergency room and hospital treatment costs can cripple a family financially, with the average stay for a respiratory ailment lasting about a week.[21] Bouts of respiratory illness and asthma attacks mean lost workdays and lost productivity. Although life is priceless, the government often monetizes loss of life when setting policies related to health and environmental protection. Using accepted valuation methodology employed by EPA in recent regulatory impact analyses, Abt Associates finds that the total monetized cost of the U.S. diesel fleet's fine particle pollution is a staggering $139 billion in 2010.



Pollution from motor vehicles, including diesels, can obscure city vistas such as illustrated in this split view of Dallas, Texas.

State and Metropolitan Area Findings

Using modeled concentrations of directly-emitted diesel fine particles throughout the lower 48 states, Abt Associates developed health impact estimates for every state and major metropolitan area in 1999, the latest year for which EPA's best emissions inventory for diesel fine particles is available.[22] Not surprisingly, heavily populated states with concentrated urban areas and significant diesel traffic fared the worst. Conversely, rural areas with a lower concentration of diesel vehicles fared much better. Similarly, metropolitan areas with large populations and heavy concentrations of diesel vehicles feel the impacts of diesel pollution most acutely.[23] In such large metropolitan areas, many hundreds of lives are shortened every year. However, because these state and metropolitan-area health estimates include only fine particles that are ***directly emitted*** from diesels – excluding any secondarily-formed particles from diesel emissions of nitrogen or sulfur oxides – they significantly understate the total adverse impact of diesel-related particles on public health.[24] Moreover, these estimates exclude any health impacts due to diesel's contribution to ozone smog.

■ States: Health Impacts from Diesel Fine Particles (1999)

Rank	State	Deaths	Cancer Deaths	Heart Attacks	Asthma Attacks	Chronic Bronchitis	Work Loss Days	Restricted Activity Days
1	New York	2,332	169	3,692	51,251	1,499	318,532	1,827,525
2	California	1,784	144	2,263	49,499	1,356	292,622	1,683,642
3	Pennsylvania	1,170	103	1,660	19,021	575	110,404	643,926
4	New Jersey	880	77	1,382	17,926	535	107,364	620,975
5	Texas	879	83	1,070	25,348	664	148,394	854,045
6	Illinois	878	76	1,193	19,162	539	112,205	649,445
7	Florida	805	77	980	13,926	438	81,462	474,601
8	Ohio	769	72	1,002	14,464	422	83,963	489,355
9	Michigan	484	43	667	10,511	299	61,109	355,260
10	Massachusetts	475	43	727	9,925	289	61,842	355,473
11	Maryland	409	39	454	8,418	246	50,275	291,675
12	Indiana	369	36	483	7,372	209	42,730	249,056
13	Georgia	329	29	377	8,514	235	51,808	298,317
14	Louisiana	324	32	339	7,131	188	40,740	236,444
15	Missouri	305	28	377	5,435	157	31,476	183,033
16	North Carolina	301	29	347	6,518	189	39,589	229,591
17	Tennessee	269	26	283	5,169	150	30,870	179,656
18	Washington	248	23	308	6,201	181	37,787	218,889
19	Virginia	248	24	303	5,991	174	36,963	214,083
20	Wisconsin	226	18	320	4,789	137	27,923	162,404
21	Arizona	214	19	268	5,215	144	30,053	173,721
22	Connecticut	206	18	340	4,091	125	24,097	140,140
23	Kentucky	198	22	213	3,764	110	22,385	130,403
24	Minnesota	193	15	291	4,713	134	27,979	161,954
25	Alabama	175	16	184	3,200	92	18,646	108,961

■ Metro Areas: Health Impacts from Diesel Fine Particles (1999)

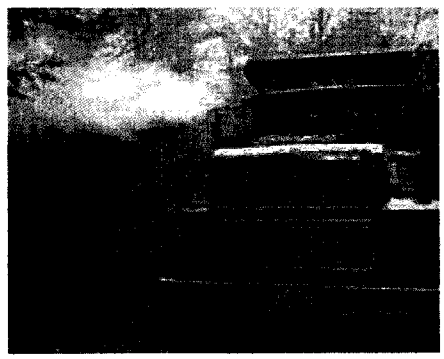
Metropolitan Area	Rank	Deaths	Cancer Deaths	Heart Attacks
New York, NY	1	2,729	202	4,342
Los Angeles, CA	2	918	72	1,193
Chicago, IL	3	755	65	1,021
Philadelphia, PA	4	727	69	990
Boston, MA	5	391	36	602
Houston, TX	6	356	35	444
San Francisco, CA	7	291	23	358
Miami, FL	8	288	23	358
Baltimore, MD	9	285	28	290
Detroit, MI	10	279	25	378
Pittsburgh, PA	11	237	21	340
Washington, DC	12	226	19	302
St. Louis, MO	13	217	20	263
Dallas, TX	14	205	19	258
Atlanta, GA	15	199	17	239
Tampa, FL	16	185	18	210
Phoenix, AZ	17	183	16	230
Cleveland, OH	18	180	15	232
Cincinnati, OH	19	171	18	218
Seattle, WA	20	165	15	208

Metropolitan Area	Rank	Deaths	Cancer Deaths	Heart Attacks
San Diego, CA	21	150	13	191
Portland, OR	22	140	13	157
Minneapolis, MN	23	133	11	205
New Orleans, LA	24	128	13	131
Riverside, CA	25	123	10	142
Baton Rouge, LA	26	102	10	109
Milwaukee, WI	27	95	8	130
Columbus, OH	28	84	9	113
Indianapolis, IN	29	82	8	107
Louisville, KY	30	82	9	91
Memphis, TN	31	81	7	79
Kansas City, MO	32	79	8	109
Providence, RI	33	76	7	119
Bridgeport, CT	34	69	6	121
Beaumont, TX	35	65	7	65
Orlando, FL	36	65	7	85
Allentown, PA	37	65	5	101
Hartford, CT	38	63	5	100
Las Vegas, NV	39	62	7	71
Virginia Beach, VA	40	62	6	65

■ Metro Areas: Per Capita Impacts from Diesel Fine Particles (1999)

Rank Based on Mortality Risk	MSA	Deaths per 100,000 Adults	Heart Attacks per 100,000 Adults	Cancer Risk per Million
1	Beaumont, TX	29	29	865
2	Baton Rouge, LA	27	29	992
3	New York, NY	25	40	959
4	Philadelphia, PA	22	29	658
5	Trenton, NJ	20	31	699
6	Baltimore, MD	19	19	584
7	Huntington, WV	18	18	477
8	New Orleans, LA	17	18	889
9	Pittsburgh, PA	15	22	415
10	Cincinnati, OH	15	19	504
11	Boston, MA	15	23	563
12	Chicago, IL	15	20	539
13	Mobile, AL	14	15	435
14	Longview, WA	14	15	441
15	Houston, TX	14	18	691
16	Allentown, PA	14	22	450
17	Cleveland, OH	14	18	416
18	Toledo, OH	14	17	423
19	Los Angeles, CA	14	18	633
20	Lancaster, PA	14	22	463
21	Scranton, PA	14	18	319
22	St. Louis, MO	14	17	405
23	Reading, PA	14	21	428
24	Lake Charles, LA	14	14	437
25	Springfield, OH	13	16	356
26	Portland, OR	13	14	488
27	Bridgeport, CT	13	22	494
28	Harrisburg, PA	12	19	412
29	York, PA	12	21	460
30	Wheeling, WV	12	14	309
31	Lebanon, PA	12	19	373
32	Evansville, IN	12	15	368
33	Memphis, TN	12	12	397
34	Savannah, GA	12	13	376
35	Dayton, OH	12	16	389
36	Vineland, NJ	12	17	365
37	Tampa, FL	12	14	365
38	Louisville, KY	12	13	384
39	Sandusky, OH	12	15	345
40	Kankakee, IL	12	14	336
41	San Francisco, CA	12	14	480
42	Muncie, IN	11	14	327
43	Duluth, MN	11	14	308
44	Michigan City, IN	11	15	370
45	Salt Lake City, UT	11	14	533
46	New Haven, CT	11	18	365
47	Steubenville, OH	11	13	279
48	Milwaukee, WI	11	15	376
49	South Bend, IN	11	15	342
50	Detroit, MI	11	15	381

The Dirty Diesel Legacy

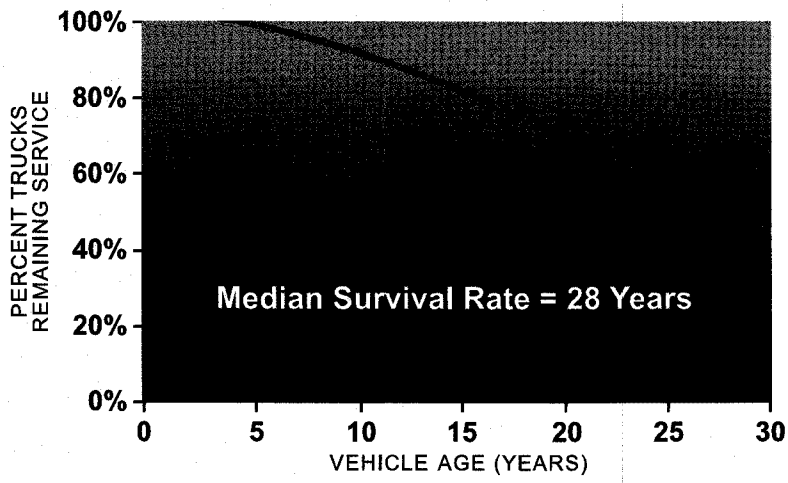


Since 1997, the U.S. EPA has promulgated major regulations that impose stringent emissions controls on new diesel vehicles, requiring tight emission standards and cleaner diesel fuel. These standards go into effect in 2007 and phase in over the next few decades. For example, the table below illustrates the progressively tighter standards for particulate matter and nitrogen oxides from trucks and buses over the next few years.

EPA Standards for New Trucks and Buses (g/bhphr)[25]

YEAR	NO_x	$PM_{2.5}$
1984	10.7	0.60
1991	5.0	0.25
1998	4.0	0.10
2004	2.0	0.10
2007	0.2	0.01

However, the emission rates of the diesel engines on the road and in use on construction sites and farms today are not affected by these rules. Considering that according to the U.S. Department of Energy the median lifetime for a heavy truck is nearly 30 years,[26] and a typical heavy duty diesel engine may power a truck for as long as one and a half million miles,[27] these vehicles will continue to pollute our air at unnecessarily high levels for years to come ***unless*** we act to clean them up now.



Median Heavy Truck Lifetime is Nearly 30 Years[28]

The Most Widespread Air Pollution Risk in the U.S.

There are few other sources of widespread pollution in our environment that rival diesel exhaust as an airborne toxin. America's 13 million diesel engines release a host of harmful substances including fine particles, ozone smog-forming nitrogen oxides, carbon monoxide, and a variety of toxic metals and organic gases such as formaldehyde, acrolein, and polycyclic aromatic hydrocarbons (PAH.)[29] In this report we focus on the respiratory, cardiovascular, and cancer effects of diesel fine particles only.[30]

Fine Particles are Linked to Heart Attacks, Asthma Attacks, and Stunted Lung Growth.

Fine particles have been linked to a wide variety of serious health impacts, from upper and lower respiratory ailments, such as asthma attacks and possible asthma onset, to heart attacks, stroke, and premature death, including crib death in children.[31] How risky is breathing air polluted with particles? A study published in the Journal of the American Medical Association found that living in the most polluted U.S. cities poses a risk similar to living with a smoker.[32] Based on thousands of studies compiled by EPA, federal health standards were established for fine particles in 1997.[34]

How Particulate Matter Kills

Fine particles, known as $PM_{2.5}$, are particles less than 2.5 microns in diameter or 1/100th the width of a human hair, so small that they are often invisible. They can be deposited deep in the lung where they can affect both the respiratory and cardiovascular systems. Researchers believe that many deaths caused by particulate matter are related to cardiovascular illness. Fine particles aggravate cardiovascular disease and trigger heart attacks by inflaming the bloodstream and initiating an inflammatory response, disrupting heart rate and increasing blood clotting. In a recent experimental study, diesel particles caused blood clots providing a plausible explanation for the increase in cardiovascular morbidity and mortality accompanying urban air pollution.[33]

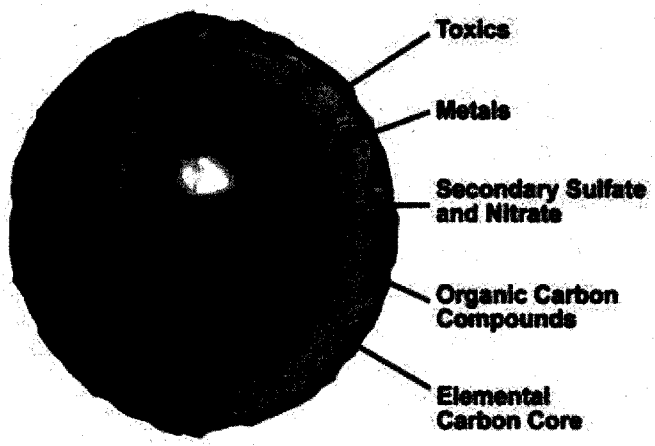
Health researchers have recently described serious health impacts of fine particles, including:

- Abnormal heart rhythms and heart attacks and atherosclerosis;[35]
- Increased incidence of stroke;[36]
- Permanent respiratory damage, characterized by fibrosis causing obstruction to airflow;[37]
- Chronic adverse effects on lung development resulting in deficits in lung function.[38]

Diesel Exhaust is a Likely Carcinogen that also Impairs Immune, Reproductive, and Nervous Systems.

In 1998, the Scientific Review Panel for the California Air Resources Board reviewed diesel exhaust as a toxic air contaminant and set a lifetime unit cancer risk from diesel particles at 3 in 10,000 persons for each microgram of annual average diesel exposure.[39] This is equivalent to 300 in a million excess lung cancers. In May 2002, EPA issued its Health Assessment for Diesel Exhaust which found diesel particulate matter to be a "likely" carcinogen. EPA did not settle on a unit risk factor but recommended a lifetime cancer risk range from 1 in 1,000 to 1 in 100,000.[40] The California unit risk falls within this range.[41]

> Diesel particles are carbon at their core with toxics and carcinogenic substances attached to their surfaces.



Applying California's cancer unit risk for diesel particulate matter to the national average concentration of directly-emitted diesel fine particles in 1999, results in a conservative estimate of 1,530 excess cases of lung cancer per year for 2005.[42] An American Cancer Society study of 150 metropolitan areas across the U.S published in 2002 supports the particulate matter cancer link.[43]

Other effects include:

- **Immune System Effects** – Diesel exposure is associated with numerous immune system responses in humans and animals culminating in increased allergic inflammatory responses and suppression of infection-fighting ability. These effects include disruption of chemical signals and production of antibodies, and an alteration in mobilization of infection-fighting cells.[44]
- **Reproductive, Developmental, and Endocrine Effects** – Diesel emissions have also been associated with reproductive, developmental and endocrine effects in animals. Specifically, diesel exposure has been associated in animals with decreased sperm production,[45] masculinization of rat fetuses,[46] changes in fetal development (thymus,[47] bone[48] and nervous system[49]) and endocrine disruption, i.e., production of adrenal and reproductive hormones.[50]
- **Nervous System Effects** – In addition to animal studies that have shown neurodevelopmental effects, a human study of railroad workers suggested that diesel exposure may have caused serious permanent impairment to the central nervous system.[51]

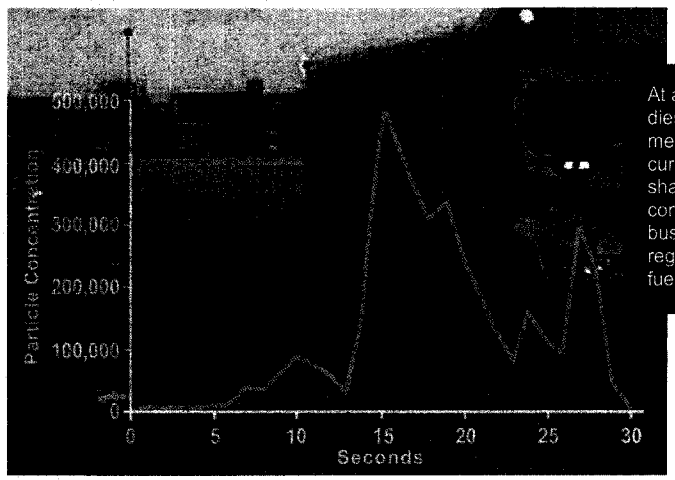
Cancer-causing Pollutants in Diesel Exhaust

Pollutant	Diesel Emissions % of all Mobile 1996[52]	EPA Carcinogen Status	Cancer Risk (per million/microgram in 70-yr life)
Formaldehyde	52%	probable	1 in a million
Acetaldehyde	56%	probable	1 in a million
Butadiene	8%	probable	2 in a million
Acrolein	80%	possible	n/a
Benzene	5%	known	2-8 in a million
Diesel Particulate Matter	77%	probable[53]	EPA: 12 to 1210 in a million; CARB: 300 in a million[54]

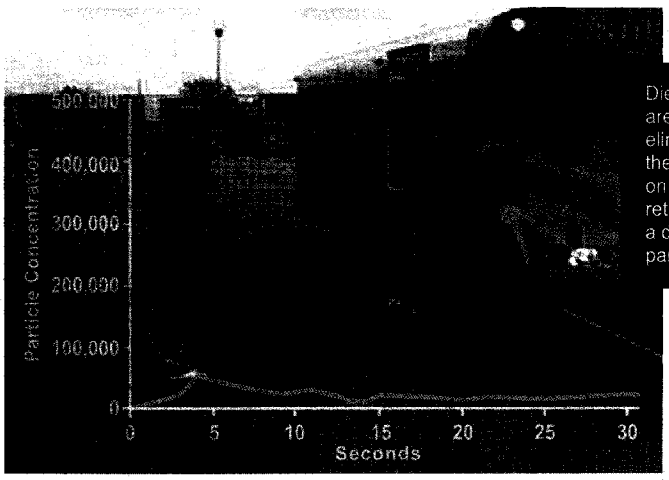
Children and Seniors are at Greatest Risk

Health researchers believe that children are more susceptible than adults to the adverse health effects of air pollution for a variety of reasons.[55] For example, children are more active than adults and therefore breathe more rapidly. Children also have more lung surface area compared to their body weight and therefore they inhale more air pound-for-pound than adults do. Compared to adults, children also have higher lung volume to body size, higher respiration rates, and spend more active time in the polluted outdoor environment. Fine particles have been linked in medical studies to serious health impacts in children such as slowed lung function growth, increased emergency room visits, increased incidences of asthma and bronchitis, and crib death. Furthermore, proximity to traffic has been linked to increased prevalence of asthma respiratory infections and allergic symptoms and asthma hospitalizations in children.[56]

Seniors are another important population at risk. Studies of the impacts of fine particles on seniors in Boston and Baltimore suggest that changes in their heart rhythms and control mechanisms occur when particle levels rise. In Phoenix, daily mortality increased in



At a bus stop, diesel particles measured at the curb spike sharply from a conventional bus running on regular diesel fuel.



Diesel particles are virtually eliminated when the bus is run on ULSD and retrofitted with a diesel particulate filter.

Children Exposed on School Buses

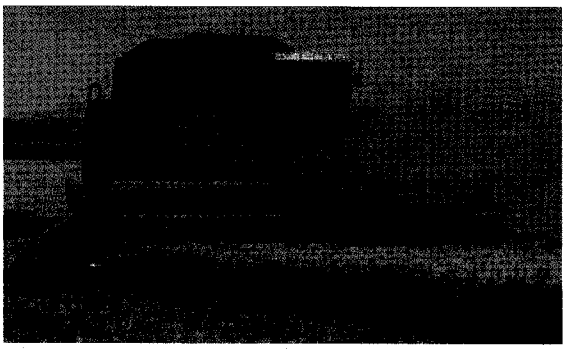
CATF Study: Cabin particulate matter eliminated with retrofit emissions controls.

Twenty four million students ride to school every day on yellow school buses that travel a total of four billion miles a year. While riding on a school bus is the safest way a student can travel to school,[57] children may be exposed to harmful pollutants, a concern since students spend an average of an hour and a half a day on school buses.[58] A recent study undertaken by Clean Air Task Force in cooperation with Purdue University investigated cabin air quality on school buses in three cities (Chicago, IL; Atlanta, GA; and Ann Arbor MI). The study found that particulate matter routinely entered the bus cabin from the tailpipe and the engine through the open front door. At some stops, particulate matter in the bus cabin exceeded levels in the outdoor air by as much as ten times. While idling or lined up in a schoolyard, rapid buildup of particulate matter in the buses also occurred. Most importantly, retrofit emissions controls worked: installation of a diesel particulate filter and the use of Ultra Low Sulfur Diesel (ULSD) fuel and a closed crankcase filtration device eliminated fine particles, ultrafine particles, black carbon and particle-bound PAH in the bus cabin. A closed crankcase filtration system by itself demonstrated major benefits and can provide immediate and low cost reductions in particulate matter levels on school buses. For a comprehensive report: **www.catf.us/goto/schoolbusreport**

seniors with increased levels of elemental and organic carbon (typical of diesels and other motor vehicles) and fine particles. Collectively, these studies demonstrate that elevated fine particle levels put the elderly at risk and suggest a possible mechanistic link between fine particles and cardiovascular disease mortality.[59]

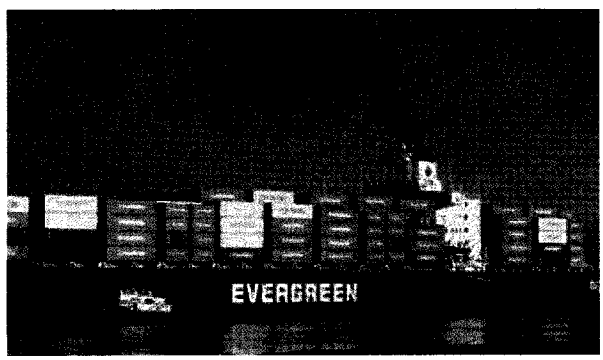
Today's Dirty Diesels

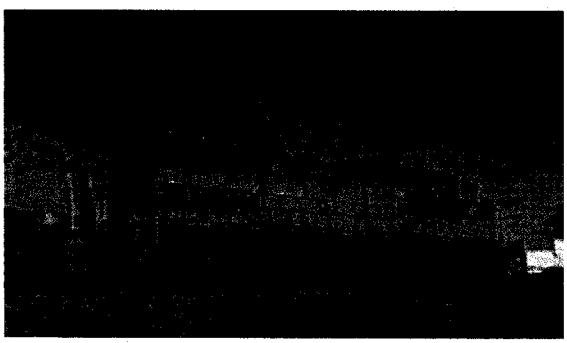
- **"On-road" or highway diesels** include many types of vehicles, such as municipal and commercial trucks and buses. Heavy duty highway diesels range from 8,500 lbs to those exceeding 60,000 lbs, such as 18-wheelers. Of the seven million diesels on the road today, 400,000 are school buses and 70,000 are transit buses. Highway diesels released 100,000 tons of directly-emitted fine particles in 2002, about one third of the total from diesels. Highway diesels also released 3.4 million tons of nitrogen oxides (NO_X) in 2002, which accounted for 16 percent of all NO_X emissions and half of all diesel NO_X emissions in the U.S. [60]



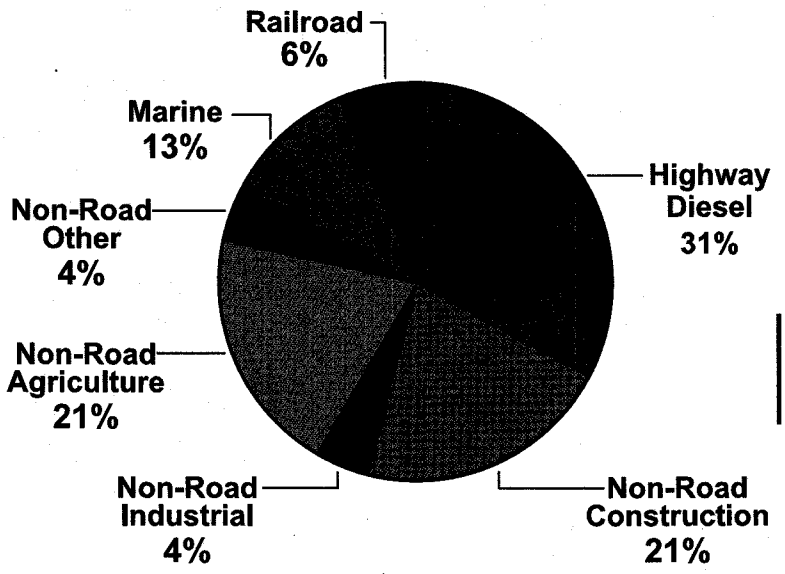
- **"Non-road" diesel engines and equipment** do not typically travel on roads or highways. There were approximately six million non-road diesel engines in service in 2003. Examples of these non-road diesels include construction equipment such as excavators, mining equipment and agricultural machinery. In 2002, 155,000 tons or half of all the fine particles directly emitted from diesels came from non-road engines. Non-road diesels also released 1.6 million tons of NO_X, 8 percent of all NO_X emissions and one quarter of all diesel NO_X emissions in the U.S. in 2002.[61]

- **Marine and river diesel** emissions are dominated by large commercial ships polluting our largest ocean and river port cities. Efforts to control pollution from shipping have focused on NO_X, although these engines also emit substantial quantities of fine particles. In 2002 marine diesel released 40,000 tons of directly-emitted fine particles, 13 percent of all diesel fine particles in the U.S. Marine diesels in the U.S. produced one million tons of diesel NO_X in 2002, 5 percent of all U.S. NO_X emissions and 14 percent of all diesel NO_X emissions.[62]





- **Locomotive diesels** account for a significant fraction of mobile source emissions in the U.S. today. In many areas, diesel trains travel through and pollute core urban and industrial areas. Diesel locomotives released 20,000 tons of directly-emitted diesel fine particles (six percent of all diesel fine particles) and 900,000 tons NO_X (13 percent of diesel NO_X). Diesel locomotives typically have a useful life of 40 years and are commonly rebuilt 5-10 times during their long service lives. For this reason, cleaning up today's locomotives is an important priority.[63]



Sources of Directly-Emitted Mobile Diesel Fine Particles

Source: EPA (2004)

Diesel "Hotspots"

Diesel Exhaust is Concentrated Near Roadways and Intersections.

Unlike industrial smokestack emissions, diesel typically is emitted at ground-level in places of concentrated population in our communities along busy streets and at our places of work. We often breathe diesel exhaust where it is fresh and most toxic. While air quality modeling, such as reported in our study, estimates average exposures in a community, your individual exposure may be much greater or smaller depending on a variety of factors. For example, the distance from where you live to major roadways and the nature of your commute to work may play a role.

Exposure to diesel exhaust is highest for those who:

- **Operate or work around diesel engines** – Occupational exposures to diesel are among the highest and have been associated with increased incidence of cancer. Furthermore, a study of diesel mechanics, train crewmen, and electricians working in a closed space near diesel generators suggests that diesel exposure may have caused both airway obstruction and serious impairment to the central nervous system. The report concludes that "impaired crews may be unable to operate trains safely."[64]
- **Live or work near areas where diesel emissions are concentrated** – Ambient diesel levels are highest near highways, busy roadways, bus depots, construction sites, railroad yards, ports and inland waterways with diesel boat traffic, major bridges, tunnels, or freight warehouses. People who live or work near these facilities face the greatest risk. Numerous recent medical studies have linked roadway proximity and traffic pollution to disease, asthma hospitalizations, and shortened life expectancy.[65] For example, a 2004 study in Ontario, Canada found increased risk of mortality from heart and lung disease in people living within 100 meters of a roadway.[66] New York City studies demonstrate that diesel trucks create air toxics hot spots at crossings, bus stops, and bus depots.[67] Rail yards can be diesel hotspots as well. For example, one study found elevated risk levels – up to 500 in a million – adjacent to a California rail yard.[68] Another study found elevated cancer risk for persons living near a ferry port.[69]

- **Regularly ride on school or transit buses, or commuter trains** – Children are exposed to elevated levels of diesel as a result of the buildup of diesel exhaust inside school buses – especially with windows closed.[70] Diesel exhaust levels on commuter trains and

People living and working near concentrated diesel emissions such as busy roadways have the greatest exposure to diesel exhaust.

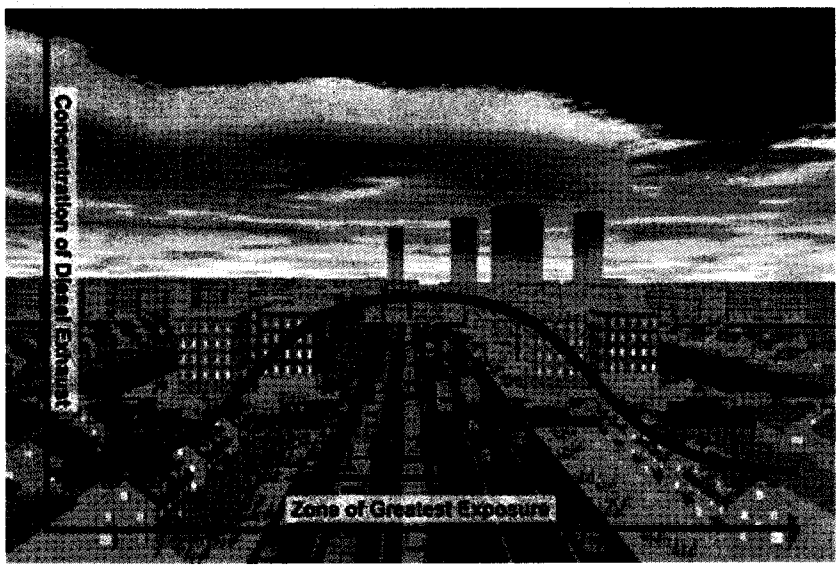


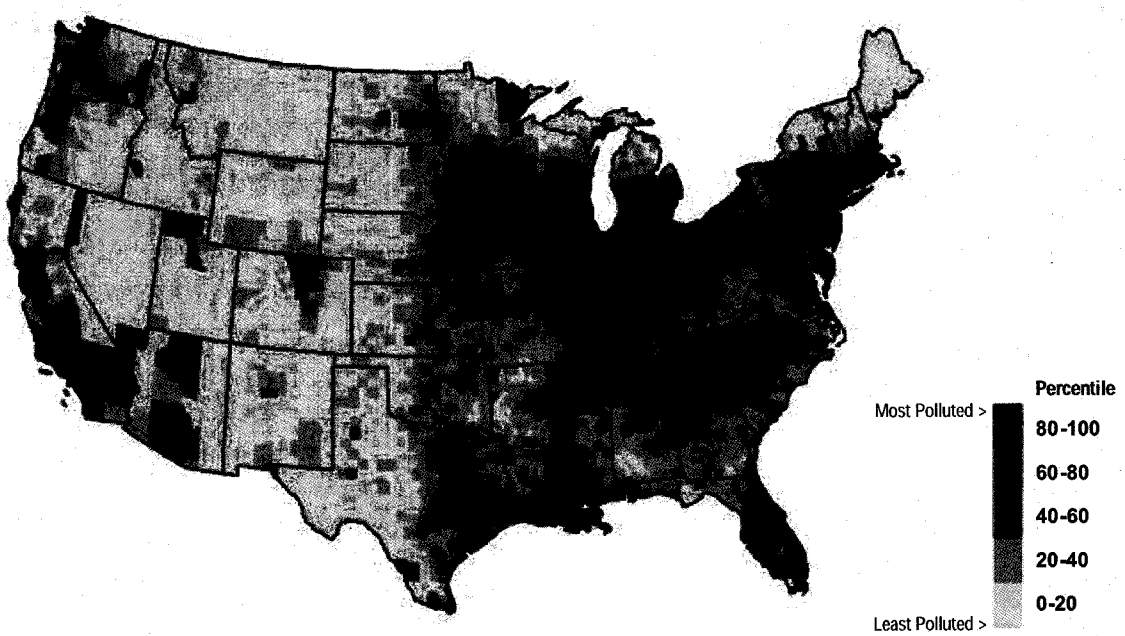
ILLUSTRATION BY ALAN MORIN

station platforms may also be high.[71]

- **Commute daily in heavy traffic** – Commuters are exposed to some of the highest diesel emissions in their cars due to pollutants released from trucks and buses on the road with them. Car occupants riding behind a diesel bus, for example, can experience extremely high levels of dangerous fine particles. Researchers in Los Angeles measured high fine particle levels (130 ug/m^3) behind an urban transit bus making numerous stops.[72] Exposures to drivers can have serious effects: a 2004 study suggests that young male state troopers experienced cardiac inflammation and heart rhythm changes from in-vehicle exposure to fine particles.[73]

Diesel exhaust from trucks and buses can be found in places we don't expect. For example it can be trapped in "urban canyons" and penetrate buildings through HVAC systems.

Exposure to diesel exhaust is also an Environmental Justice issue. Concentration of minority and low-income populations are more likely to be found in cities near diesel sources. Because these neighborhoods are exposed to some of the highest diesel exhaust levels, residents are certain to experience disproportionate health impacts.



Directly-Emitted Diesel Fine Particle Concentrations by County in the U.S. (1999)

A Solution Within Our Reach

Diesel Fine Particles Can Be Virtually Eliminated by Emission Controls Available Today.

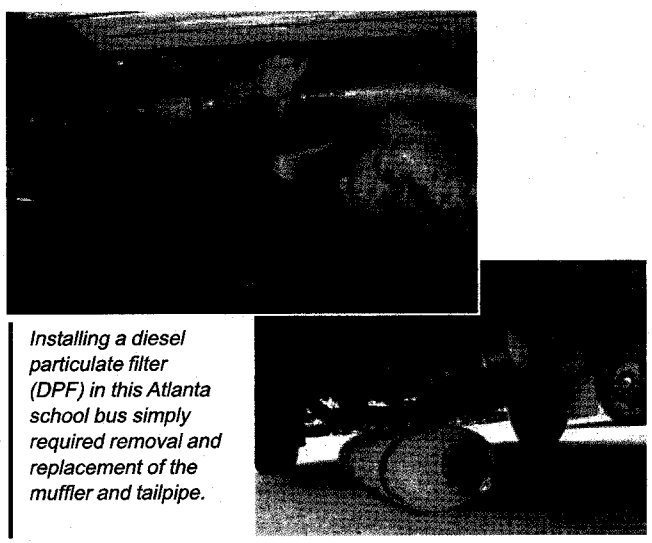
Virtually all of the health risk posed by diesel exhaust can be eliminated through the application of emissions control strategies available today. For example, an aggressive but feasible program to reduce diesel particle emissions nationwide 50 percent by 2010, 75 percent by 2015, and 85 percent by 2020 would save about 100,000 lives between now and 2030 – beyond those lives that will be saved under EPA's new engine regulations.[74] Adopting this as a national goal would help states and municipalities set milestones for improvement and would be consistent with EPA's recently announced goal of retrofitting the entire U.S. fleet of diesel vehicles by 2015.[75] Indeed, California has already set a Diesel Risk Reduction goal of 75 percent 2010 and 85 percent by 2020. Over the last few years the California Air Resources Board has begun to issue regulations to achieve these goals.[76]

"Retrofit, Rebuild, Replace"

A variety of practical strategies exist to reduce diesel particle levels in America: tailpipe retrofits, clean fuels, closed crankcase filtration systems, engine rebuild and replacement requirements, emission specifications for vehicles used in public works contracts, anti-idling ordinances and legislation, truck stop electrification programs, aggressive fleet turnover policies, and more.

The most cost-effective approach to reducing diesel exhaust is likely in many cases to be the direct application of retrofit technology. Although the purchase of new, much cleaner vehicles will remain an important remedial strategy, the replacement of the entire diesel fleet is an expensive proposition that will have to be phased in over time. What's more, we can meet the challenge of reducing fine particles and related air toxics without replacing all vehicles right now. Current technology can easily remove particles from diesel exhaust. Retrofits that eliminate over 90 percent of fine particles from a heavy duty diesel bus engine typically cost $3,000-$7,500. This is a small expenditure when compared to the typical $60,000-75,000 price tag for a new school bus or $300,000 for a transit bus.[77]

Retrofits are available from many engine manufacturers. They generally are easy to install especially on highway vehicles. Nonetheless, it is important to point out that retrofits are not a "one size fits all" proposition. Retrofitting a fleet calls for careful planning and, often, a mix of strategies that will depend on the make and model year of the engines being retrofitted and funds available. For example, some heavy-duty engines lack modern electronic engine controls and are therefore are too old for some retrofit devices. Other diesel equipment simply does not have space for retrofit installation. Duty cycle is an important consideration too. Some engines do not run constantly which means that catalytic retrofit devices requiring consistent high engine temperatures do not operate as efficiently. Furthermore, some engines release pollution from crankcase ventilation in addition to the tailpipe. This calls for additional strategies. For some vehicles and model years, replacement may be the best option. As a result, fleets will need to develop individualized strategies that optimize emission reduction from their vehicles and equipment. Fortunately, this is not hard to do.



Installing a diesel particulate filter (DPF) in this Atlanta school bus simply required removal and replacement of the muffler and tailpipe.

Catalyzed diesel particulate matter filters (DPF) can reduce emissions of fine particles and adsorbed air toxics by over 90 percent. DPFs have been used in thousands of on- and non-road diesel applications. Diesel oxidation catalysts (DOCs) represent a less expensive albeit less effective option. They are smaller and therefore easier to install. EPA has verified that they can reduce total particulate matter emissions by 10-30 percent. Like the DPF, the DOC is also attached to the exhaust system. Installing one on a diesel truck or bus costs about $1,000. DOCs may be appropriate for vehicles built before 1995 that lack electronic controls and for construction equipment where there is inadequate space for a DPF to be installed. DOCs have been installed in more than 1.5 million trucks in the U.S.[78]

Low Sulfur Diesel Fuels Are Requisite for Effective Retrofit Controls.

Diesel particulate filters require low sulfur fuels because sulfur in the fuel can foul the emission control device. Unfortunately, low sulfur fuels are not available everywhere in the U.S. today (see http://www.epa.gov/otaq/retrofit/fuelsmap.htm for the current fuel availability map). Where ULSD is available, decision makers should consider requiring installation of filters where possible. Federal regulations have established diesel fuel and additive formulation requirements for on-road vehicles, limiting fuel sulfur content to 15 ppm nationwide beginning in 2006 for use with 2007 highway vehicles. Starting in 2010, non-road equipment will be required to use ULSD.

Biodiesel is another potential low-sulfur fuel choice that can achieve modest reductions in emissions when used as a blend, or higher reductions when used at 100 percent. Biodiesel is an alternative diesel fuel made from either animal fats or plants such as soybeans.

Ultra low sulfur diesel fuel will be available nationwide mid-2006.

Cleaning up All School Buses Within a Decade

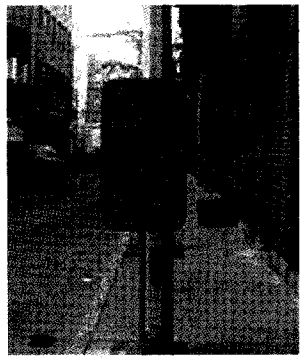
With today's emissions controls, students need not be exposed to diesel exhaust while riding to school. EPA in the summer of 2004 announced the goal of retrofitting all existing school buses with pollution controls within a decade.[79] Funding retrofits and cleaner fuel presents the greatest obstacle facing school districts. To achieve this goal, adequate funds must be appropriated by states and the federal government.

Recommendations

Cities and States Must Act to Reduce Diesel.

The fine particle pollution problem is so widespread in the U.S. about one quarter of the U.S. population resides in areas that violate the standard. EPA recently formally designated over 200 counties in "nonattainment" with the annual fine particle standard.[80] Countless additional commuters may also spend significant time in areas exceeding the standard where they work. But the rest of the country is not safe from the risk posed by diesel particles – science tells us that particle-related health impacts don't stop once the standard is achieved. Health research has shown that there are adverse health impacts from particles even at very low concentrations.[81]

Cities and states that have been designated as "nonattainment" must act now to achieve meaningful reductions in fine particles. For those areas, state implementation plans must be developed and presented to EPA for approval within three years. Controls must then be implemented and air quality standards achieved by 2010. For this reason, states and cites must start now to determine how to achieve substantial emissions reductions. With rules to reduce particles from power plants pending at EPA and expected to be finalized in the near future, diesel emissions will become the largest remaining share of the problem and the most cost-effective solution, one that largely is within the control of states and municipalities.



MA TURNPIKE AUTHORITY

Cities should adopt and enforce anti-idling ordinances.

Cities and states should:

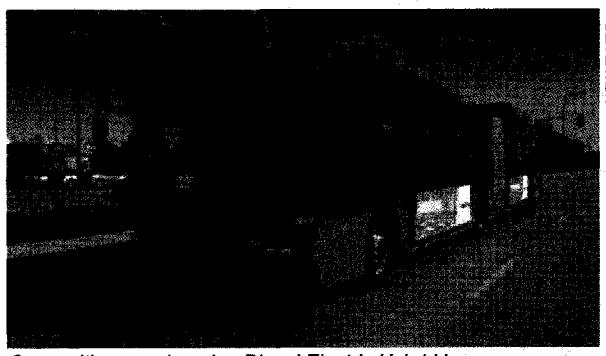
- Establish ambitious goals for reducing risk to their citizens by cleaning up existing diesels;
- Identify priority geographic areas and diesel "hotspots" for immediate attention;
- Adopt a package of options for reducing diesel exhaust including:
  - Retrofits accomplished by replacing mufflers with an optimal mix of filters or oxidation catalysts depending on vehicle age and type;
  - Requiring Ultra Low Sulfur Diesel and cleaner alternative fuels;
  - Closed crankcase ventilation systems to eliminate engine exhaust from penetrating the cabins of school and transit buses;
  - Engine rebuild and replacement requirements;
  - Truck stop electrification programs to give long-haul truckers a way to power their rigs overnight without running their engines;
  - Contract specifications requiring cleanup of trucks and construction equipment used in public works projects.
- Adopt diesel cleanup measures as federally-enforceable requirements in State Implementation Plans (SIPs) for the attainment of the fine particle and ozone air quality standards;
- Create and fund programs to provide money for diesel equipment owners to replace or rebuild high-polluting diesel engines;
- Adopt and enforce anti-idling ordinances and legislation.

To meet this challenge, several states and cities have begun to take action. California continues to lead the way in reducing diesel emissions: adopting stricter fine particle air quality standards, developing a statewide diesel risk reduction plan, and establishing a state program to clean up on- and non-road diesel engines ranging from garbage trucks to stationary generators.[82] When completed, the California program will regulate emissions from all existing diesels within its jurisdiction.

Trucks parked at New York Thruway rest area shut off their engines and plug into IdleAire facility for heat and electricity.

In New York, over 120,000 kids now ride a school bus that has had a retrofit kit installed to reduce diesel emissions. Under city and state law all New York City-sponsored construction projects are required to use ULSD and all heavy equipment engines at the sites must be retrofitted. Likewise, Seattle, King County, and the State of Washington have made a solid start on diesel cleanup from on- and non-road vehicles, and ships including a commitment to retrofit up to 8,000 school buses using local, state, federal, and SEP monies and buy up to 250 new diesel/electric hybrid buses. Other cities also have made a start.[83]

California and Texas have created funds – the "Carl Moyer" program in California and the Texas Emission Reduction Program (TERP) – to provide funding for diesel equipment owners to replace or rebuild high-polluting diesel engines.



NEW FLYER

Some cities are choosing Diesel Electric Hybrid buses as an alternative to conventional diesel buses.

Washington Must Support States

States and cities cannot meet the challenge of diesel pollution alone. U.S. EPA has recognized the dangers and societal costs of diesel exhaust and set tighter emission standards for new highway and non-road diesel engines and mandated the availability beginning in 2006 of Ultra Low Sulfur Diesel (ULSD) fuel nationwide. These requirements must be retained with no backsliding. In addition, EPA has set a national goal of cleaning up all of America's existing diesels by 2015 and has established a voluntary retrofit program to begin to meet it.[84] However, this challenge will only be met with an aggressive set of policies and adequate funding to ensure the goal can be accomplished.

Many states do not have the resources to clean up state and municipally-owned vehicles. They will need the support of the federal government to achieve EPA's goal.

Federal action may also be needed to clean up transient diesel vehicles, including long-haul trucks, marine diesel shipping in U.S. ports, and locomotives that typically travel from city to city dispersing their emissions along travel corridors. Because the Clean Air Act contains limited authority for EPA to establish national diesel retrofit rules, federal legislation will ultimately be needed to establish federal requirements and funding for a national retrofit program for all diesel engines as well as these interstate diesels.

The Federal government should:

- Pass legislation providing funding for the cleanup of municipal and state fleet vehicles;
- Explore regulatory options for reducing emissions from existing interstate fleets such as long-haul trucks, shipping, and locomotives;
- Retain and enforce the tighter new engine and cleaner fuel standards for highway and non-road diesels.

Endnotes

1 Wilson, Richard and Spengler, John, eds. *Particles in Our Air: Concentrations and Health Effects* (1999) p. 212.

2 Schwartz, J.,"Air Pollution Deadlier than Previously Thought," Harvard School of Public Health, Press Release, March 2, 2000.

3 Laden, F., Neas, L., Dockery, D. and Schwartz, J., *Association of Fine Particulate Matter from Different Sources with Daily Mortality in Six U.S. Cities,* Environmental Health Perspectives, Vol. 108, No. 10, (2000) p. 941-947.

4 Nemmar, A. et al., *Passage of Inhaled Particles Into the Blood Circulation in Humans.* Circulation, Vol. 105, (2002), 411-414 ; Donaldson, Ken, et al., *Ambient Particle Inhalation and the Cardiovascular System: Potential Mechanisms,* Envir. Health Perspectives, Vol. 109, Supp. 4, Aug. 2001, p. 525.1

5 National Center for Environmental Assessment, Office of Research and Development, U.S. EPA. EPA/600/8-90/057F. May 2002. International Agency on Cancer, Monograph 46. See at: http://www-cie.iarc.fr/htdocs/monographs/vol46/46-01.htm; California Air Resources Board (1998) Proposed Identification of Diesel Exhaust as a Toxic Air Contaminant; See also, California Environmental Protection Agency, Air Resources Board, Office of Environmental Health Hazard Assessment, April 22, 1998; CalEPA (2002). Health Assessment for Diesel Engine Exhaust;

6 American Academy of Pediatrics, Committee on Environmental Health, *Ambient Air Pollution: Health Hazards to Children,* Pediatrics, Vol 114, No. 6, (December 2004) pp. 1699-1707. Available at www.pediat rics.org. For a complete summary of studies of particulate matter and health see: EPA Air Quality Criteria for Particulate Matter, October 2004 avaialble at: http://cfpub.epa.gov/ncea/cfm/partmatt.cfm

7 Modeled health impacts of less severe acute health impacts (e.g. other than mortality, heart attacks) likely understate the full magnitude of the impacts because many cases go unreported (e.g. asthma, bronchitis self-treatment, or treatment in small clinics or private offices.) Furthermore, the U.S. does not manage a central database of national health records.

8 U.S. EPA, OAR, "Final Report to Congress on Benefits and Costs of the Clean Air Act,1970-1990," EPA 410-R-97-002, (1997) page I-23 at http://www.epa.gov/air/sect812/appen_i.pdf.

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11 U.S. Department of Transportation, National Highway Traffic Safety Administration *Traffic Safety Facts 2000: Occupant Protection* (Washington, D.C. 2001). Available online at: http://www.bts.gov/publications/transportation_statistics_annual_report/2001/html/chapter_06_figure_01_152_table_.html

12 This analysis is based on methodology approved by U.S. EPA's Science Advisory Board and used by EPA in the Regulatory Impact Analysis (RIA) of the non-road rule. EPA Final Regulatory Impact Analysis, "Control of Emissions from Nonroad Diesel Engines," EPA420-R-04-007. (May 2004) http://www.epa.gov/nonroad-diesel/2004fr/420r 04007.pdf. It begins with EPA emissions inventory data, models the dispersion of those emissions using the Regional Emissions Modeling System for Acid Deposition (REMSAD) air quality model, and then applies a damage function model using concentration-response relationships to estimate adverse health endpoints from modeled changes in air quality. This analysis estimates the adverse health endpoints attributable to diesel PM2.5 in the year 2010. For a summary of CATF's methodology and FAQs please go to www.catf.us/goto/dieselhealth/ and click on "learn more." For Abt Associates' ASPEN and REMSAD reports please see: www.catf.us/goto/AbtASPEN/ and www.catf.us/goto/AbtREMSAD/.

13 Estimate is based on EPA methodology described in EPA Memorandum, Bryan Hubbell to Sam Napolitano, July 2, 2001. Estimated NO_x, SO_2 and PM emissions health damages for heavy duty vehicle emissions.

14 Through only those diesel regulations promulgated to date, California will reduce diesel fine particles by 30 percent from year 2000 levels. California has announced plans to promulgate additional critical regulations in the next few years to address significant sources such as construction, agriculture, and inland shipping. California Air Resources Board (CARB) 2004a. Air Quality Almanac Emission Projections. Online at http://www.arb.ca.gov/emisinv/emsmain/emsmain.htm; California Air Resources Board (CARB). 2003a. Staff Report: Initial Statement of Reasons: Proposed Diesel Particulate Matter Control Measure for On Road Heavy-Duty Residential and Commercial Solid Waste Collection Vehicles. Sacramento, CA: California Environmental Protection Agency. California Air Resources Board (CARB) 2003b Staff Report: Initial Statement of Reasons for Proposed Rulemaking: Airborne Toxic Control Measure for Stationary Compression Ignition Engines. Sacramento, CA: California Environmental Protection Agency, Stationary Source Division Emissions Assessment Branch;. California Air Resources Board (CARB) 2003c. REVISED – Staff Report: Initial Statement of Reasons for Proposed Rulemaking: Airborne Toxic Control Measure for In-use Diesel Fueled Transport Refrigeration Units (TRU) and TRU Generator Sets, and Facilities Where TRUs Operate. Sacramento, CA: California Environmental Protection Agency, Stationary Source Division Emissions Assessment Branch. The Union of Concerned Scientists recently estimated the costs and benefits of achieving the CARB Diesel Risk Reduction goal. See Union of Concerned Scientists, *Sick of Soot: Reducing the Health Impacts of Diesel Pollution in California* (June 2004) available online at: http://www.ucsusa.org/clean_vehicles/trucks_and_buses/page.cfm?pageID=1429

15 This analysis was performed by multiplying modeled ASPEN (Assessment System for Population Exposure Nationwide) 1999 county-level ambient diesel PM2.5 concentration data times: (1) the upper and lower bounds of EPA's possible diesel particulate matter cancer risk range; and (2) the California Air Resources Board diesel cancer unit risk factor. See: California Diesel Risk Reduction Plan: http://www.arb.ca.gov/diesel/documents/rrpapp.htm; EPA, Health Assessment Document for Diesel Exhaust, Office of Research and Development, EPA/600/8-90/057F (May 2002). The United States Public Interest Research Group previously used

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16 "The estimated possible risk ranges (10^{-5} to 10^{-3} as well as lower and zero risk) provide a perspective of the potential significance of the lung cancer hazard." EPA, Health Assessment Document for Diesel Exhaust, Office of Research and Development, EPA/600/8-90/057F (May 2002) at p. 8-15. For CARB unit risk value, see: Findings of the Scientific Review Panel on *The Report on Diesel Exhaust* as adopted at the Panel's April 22, 1998, meeting. http://www.arb.ca.gov/toxics/dieseltac/defnds.pdf. See also, http://www.arb.ca.gov/regact/diesltac/diesltac.htm. The findings in this report based on the CARB unit risk factor are consistent with EPA's possible diesel risk range e.g., 3×10^{-4} is within EPA's range of 10^{-3} to 10^{-5}.

17 The number per million is the chance in a population of a million people who might be expected to get cancer over a 70-year lifetime. A potential cancer risk of 10 in a million means if one million people were exposed to a certain level of a pollutant or chemical there is a chance that 10 of them may develop cancer over their 70-year lifetime. This would be 10 new cases of cancer above the expected rate of cancer in the population. According to CARB the expected rate of cancer for all causes, including smoking, is about 200,000 to 250,000 chances in a million (one in four to five people).

18 For 1999 NATA national excess cancer risk from air toxics other than diesel see: Inside EPA, Inside Washington Publishers, (December 15, 2004) http://www.insideepa.com/

19 This finding is based on inhalation as the only exposure path and is limited to the thirty-three air toxics included in EPA's National Air Toxics Assessment (NATA). The relative cancer risk of diesel particulate matter is calculated as a ratio of the cancer risk of all air toxics tracked by EPA in the NATA divided by the risk of diesel particulate. We calculated the cancer risk for diesel PM in the U.S. based by applying the CARB cancer unit risk factor for diesel particulate matter to 1999 ASPEN model average national ambient concentration results for diesel PM. (Source for national toxic risk: Inside EPA, Inside Washington Publishers, December 15, 2004.)

20 According to the EPA's categorization of counties as urban or rural, the average ASPEN 1999 ambient diesel fine particle concentration is 1.3822 ug/m^3 for urban counties and 0.4730 ug/m^3 for rural counties. The overall national average is 1.2096 ug/m^3. These averages are population weighted. These averages convert (using the 0.0003 factor) to cancer risks of 415 per million urban, 142 per million rural, and 363 per million average.

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24 The state and metropolitan area health effects reported here exclude those associated with secondarily-formed fine particles, i.e., particles formed from gaseous emissions through post-emission atmospheric chemical reactions. Typically, these include nitrate from nitrogen oxide emissions and sulfate from sulfur dioxide emissions. Secondarily-formed fine particles may make up as much as one-third of diesel-related particles. See Lloyd, A. C., and Cackette, T.A. (2001). Diesel engines: Environmental Impact and Control. Journal of Air and Waste Management Association, v. 51, p. 809-847, June 2001.

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76 California Air Resources Board (CARB) 2004a. Air Quality Almanac Emission Projections. Online at *http://www.arb.ca.gov/emisinv/emsmain/emsmain.htm;* California Air Resources Board (CARB). 2003a. Staff Report: "Initial Statement of Reasons: Proposed Diesel Particulate Matter Control Measure for On-Road Heavy-Duty Residential and Commercial Solid Waste Collection Vehicles," California Environmental Protection Agency, Sacramento, CA; California Air Resources Board (CARB) 2003b Staff Report: "Initial Statement of Reasons for Proposed Rulemaking: Airborne Toxic Control Measure for Stationary Compression Ignition Engines," Sacramento, CA: California Environmental Protection Agency, Stationary Source Division Emissions Assessment Branch; California Air Resources Board (CARB) 2003c. REVISED – Staff Report: Initial Statement of Reasons for Proposed Rulemaking: Airborne Toxic Control Measure for In-use Diesel Fueled Transport Refrigeration Units (TRU) and TRU Generator Sets, and Facilities Where TRUs Operate, Sacramento, CA: California Environmental Protection Agency, Stationary Source Division Emissions Assessment Branch.

77 MECA: http://www.epa.gov/otaq/retrofit/documents/meca1.pdf; CARB cost-effectiveness analysis: http://www.arb.ca.gov/regact/bus02/appf.pdf

78 MECA: http://www.meca.org/jahia/Jahia/engineName/filemanager/pid/229/dieselfact.PDF?actionreq=actionFileDownload&fileItem=213. A newly verified Diesel Oxidation Catalyst technology, called "a torturous path filter" achieves a 50 percent reduction in diesel particulate at about half the cost of a diesel particulate filter.

79 Motor Age, "EPA to Retrofit 11 Million Diesels," Advanstar Communications (August 2004). Available online at: http://www.motorage.com/motorage/article/articleDetail.jsp?id=141102. See also, http://www.epa.gov/cleanschoolbus/

80 See: http://www.epa.gov/air/oaqps/particles/designations/index.htm

81 Vedal, S., Brauer, M., White, R., and Petkau, R., (2003). Air Pollution and Daily Mortality in a City With Low Levels of Air Pollution, Environmental Health Perspectives Vol.111, No.1, (2003), pp. 45-51.

82 See: California Risk Reduction Plan at: http://www.arb.ca.gov/diesel/documents/rrpfinal.pdf

83 For more information about retrofit programs in your area see: http://www.epa.gov/otaq/retrofit/projectmap.htm

84 For more information on EPA's Voluntary Retrofit Program see: http://www.epa.gov/otaq/retrofit

CLEAN AIR TASK FORCE

18 Tremont Street, Suite 530
Boston, MA 02108
Tel: 617-624-0234 / Fax: 617-624-0230

www.catf.us

BOARD MEETING DATE: April 2, 2010
AGENDA NO. 25

PROPOSAL:

Annual Meeting of the Brain & Lung Tumor and Air Pollution Foundation

SYNOPSIS:

This item is to conduct the annual meeting of the Brain & Lung Tumor and Air Pollution Foundation. The Foundation staff will present an annual report detailing the research supported by the Foundation over the past year, the Foundation's plans for the future, and a financial report.

COMMITTEE:

Not Applicable

RECOMMENDED ACTIONS:

Receive and file the annual report and ratify the Foundation disbursements described in the annual report.

Barry R. Wallerstein, D.Env.
Executive Officer

2009 Annual Report

1. Background

In February, 2003, the Board established the Brain Tumor and Air Pollution Foundation. In March, 2004 the Foundation amended its Articles of Incorporation to change its name to Brain & Lung Tumor and Air Pollution Foundation and to specify that its purpose is related to the effects of air pollution on brain and lung cancer. The mission of the Foundation is to support research studies on the association between air pollution and brain and lung cancer, as well as research for the development of novel therapeutics for such tumors. To carry out its purpose, the Foundation has funded research projects investigating the links between air pollution and brain and lung tumors. The dollar amount of the funding received to date is $3,722,568. The current projects are described below.

2. Directors and Officers

The Directors of the Foundation are:	Michael D. Antonovich, Chairman Dennis Yates, Vice Chairman Bill Campbell Dr. Thomas Godfrey Josie Gonzalez
The Foundation's staff is:	Barry Wallerstein, Chief Executive Officer Denise Whitcher, Secretary Lisa Virgo, Treasurer

3. Report on the Foundation's Activities

Current Research Projects

In 2008, the Foundation Board approved funding for the following projects.

A. Brain Tumors and Air Pollution
Principal Investigator: Dr. Keith Black, Cedars Sinai Medical Center
Approved Funding: $1,250,000
Allocated Funding: $625,000

In previous studies funded by the Foundation, the researchers discovered that the activities of several genes were altered in laboratory animals exposed to concentrated ambient particulate pollutants. These genes may play a significant role in the development of brain tumors. In the new study, a more detailed analysis at the molecular level is being conducted. Individual areas of the brain, as well as other organs, are being included to determine if there are specific tissue types that are affected by particulate matter exposures. The research is being done in collaboration with the UC Irvine School of Medicine. This project is currently ongoing, and a report of results is expected by the end of this year.

B. Childhood Brain Tumors and Air Pollution
Principal Investigator: Roberta McKean-Cowdin, Ph.D., USC School of Medicine
Approved Funding: $220,000
Allocated Funding: $199,627

In a preliminary epidemiologic investigation on the potential role of air pollution with brain tumor risk funded by the Foundation, the researchers found a significant association of risk of brain tumors in children and exposure to PM2.5. The study population included children between the ages of 0-5 years diagnosed with brain tumors from in Los Angeles, Orange, Riverside, and San Bernardino counties from 1991 through 2002. This new study is conducting additional analyses including more detailed estimates of PM2.5 exposure based on geospatial extrapolations of monitoring data, and also includes distance of residential address from roadways as an estimate of exposure to traffic-related pollutant emissions. The study population is being expanded to include data from the West Coast Childhood Brain Tumor study. The latter database includes children aged 1-19 years diagnosed with brain tumors in Los Angeles county from 1984

through 1991. This project is currently ongoing, and a report of results is expected by the end of this year.

4. Financial Report

As of December 31, 2009, the Foundation had a cash balance of $689,263. Following is an accounting of the Foundation's operations since its inception (7/23/03):

Revenue from Operations	
Contributions	$3,722,568
Interest Income	36,256
Total Revenue from Operations	***$3,758,824***
Operating Expenses	
Grants Awarded	
-Cedars-Sinai	$2,684,250
-USC	377,967
Corporation Filing Costs	820
Bank charges	524
Professional fees-audit	6,000
Total Operating Expenses	***$3,069,561***
Cash Balance, 12/31/09	**$689,263**

5. Plans for Upcoming Year

The Foundation will continue monitoring the progress of existing research projects. The Foundation will evaluate potential new projects and provide funding to the extent that additional funds become available.

The Foundation Board asked that any funds transferred to the Health Effects Research Fund by the AQMD Governing Board be reserved for the Foundation's use to support brain and lung tumor and air pollution research, but not transferred until specific projects are identified by the Foundation Board. The Foundation Board also asked staff to prepare a plan for future research.

Technical Support Document for Cancer Potency Factors:

Methodologies for derivation, listing of available values, and adjustments to allow for early life stage exposures.

April 2009

California Environmental Protection Agency

Office of Environmental Health Hazard Assessment

Air Toxicology and Epidemiology Branch

Prepared by:

John D. Budroe, Ph.D.

James F. Collins, Ph.D.

Melanie A. Marty, Ph.D.

Andrew G. Salmon, M.A., D. Phil.

Joseph P. Brown, Ph.D.

Air Toxicology and Epidemiology Branch

and

Martha S. Sandy, Ph.D., M.P.H.

Claire D. Sherman, Ph.D.

Rajpal S. Tomar, Ph.D.

Lauren Zeise, Ph.D.

Reproductive and Cancer Hazard Assessment Branch,

Office of Environmental Health Hazard Assessment

Reviewed By

George V. Alexeeff, Ph.D., Deputy Director

Melanie A. Marty, Ph.D., Chief, Air Toxicology and Epidemiology Branch

Lauren Zeise, Ph.D., Chief, Reproductive and Cancer Hazard Assessment Branch

EXECUTIVE SUMMARY

The Air Toxics "Hot Spots" Information and Assessment Act (AB 2588, Connelly) was enacted in September 1987. Under this Act, stationary sources of air pollution are required to report the types and quantities of certain substances their facilities routinely release into the air. The goals of the Air Toxics "Hot Spots" Act are to collect emission data, identify facilities having localized impacts, ascertain health risks posed by those facilities, notify nearby residents of significant risks and reduce emissions from significant sources.

The Technical Support Document for Cancer Potency Factors (TSD) contains cancer unit risks and potency factors for 107 of the 201 carcinogenic substances or groups of substances for which emissions must be quantified in the Air Toxics Hot Spots program. These unit risks are used in the cancer risk assessment of facility emissions.

The purposes of this revision to the TSD is to provide updated calculation procedures used to derive the estimated unit risk and cancer potency factors, and to describe the procedures used to consider the increased susceptibility of infants and children compared to adults to carcinogens. This updates cancer risk assessment methods originally laid out in the California Department of Health Services' Guidelines for Chemical Carcinogen Risk Assessment (CDHS, 1985), and more recently summarized in the previous Hot Spots technical support document Part II (OEHHA, 2005a). Summaries of cancer potency factors and the underlying data are provided in Appendix A and B. [these did not undergo revision and are not included in this review package.]

The procedures used to consider the increased susceptibility to carcinogens of infants and children as compared to adults include the use of age-specific weighting factors in calculating cancer risks from exposures of infants, children and adolescents, to reflect their anticipated special sensitivity to carcinogens

This document is one part of the Air Toxics Hot Spots Program Risk Assessment Guidelines. The other documents originally included in the Guidelines are Part I: Technical Support Document for the Determination of Acute Toxicity Reference Exposure Levels for Airborne Toxicants; Part III: Technical Support Document for Determination of Noncancer Chronic Reference Exposure Levels; Part IV: Technical Support Document for Exposure Assessment and Stochastic Analysis; Part V: Air Toxic Hot Spots Program Risk Assessment Guidelines. As a part of the same revision process which led to production of this revised TSD on cancer potencies, the original TSDs for Acute and Chronic Reference Exposure Levels have been replaced with a new unified TSD for Acute, 8-hour and Chronic Reference Exposure Levels.

The major changes to the TSD include the following:

- Based on the OEHHA analysis of the potency by lifestage at exposure, OEHHA proposes weighting cancer risk by a factor of 10 for exposures that occur from birth to 2 years of age, and by a factor of 3 for exposures that occur from 2 years through 15 years of age. We propose to apply this weighting factor to all carcinogens, regardless of purported mechanism of action, unless chemical-specific data exist to the contrary. In cases where

there are adequate data for a specific carcinogen of potency by age, we would use the data to make any adjustments to risk.

- OEHHA proposes to use the Benchmark Dose method to compute potency factors rather than the more traditional linearized multistage model (LMS), although the LMS will still be used in some instances. The BMDL model essentially uses an empirical fit to the data (usually best with the multistage model), and then extrapolates with a straight line from the 95 % lower confidence limit of the BMD (BMDL) to zero. This method is simpler and does not assume any underlying theoretical mechanisms at the low dose range. The BMDL method results in very similar estimates of potency as the LMS method.

- OEHHA will use scaling based on body weight to the ¾ power, rather than to the 2/3 power.

- OEHHA's evaluations of the carcinogenicity of chemicals generally follow the guidelines laid out by IARC for identification and classification of potential human carcinogens, which are described in detail in the most recent revision of the *Preamble* to the IARC monographs series (IARC, 2006).

PREFACE

The Air Toxics "Hot Spots" Information and Assessment Act (AB 2588, Connelly) was enacted in September 1987. Under this Act, stationary sources are required to report the types and quantities of certain substances their facilities routinely release into the air. The goals of the Air Toxics "Hot Spots" Act are to collect emission data, identify facilities having localized impacts, ascertain health risks posed by those facilities, notify nearby residents of significant risks and reduce emissions from significant sources.

The Technical Support Document for Cancer Potency Factors (TSD) contains cancer unit risks and potency factors for 107 of the 201 carcinogenic substances or groups of substances for which emissions must be quantified in the Air Toxics Hot Spots program. These unit risks are used in risk assessment of facility emissions. The TSD provides updated calculation procedures used to derive the estimated unit risk and cancer potency factors, and procedures to consider early-life susceptibility to carcinogens. Summaries of cancer potency factors and the underlying data are provided in Appendix A and B. [these did not undergo revision and are not included in this review package.]

In this document, OEHHA is responding to the requirements of the 1999 Children's Environmental Health Protection Act, (SB25, Escutia) by revising the procedures for derivation and application of cancer potency factors to take account of general or chemical-specific information which suggests that children may be especially susceptible to certain carcinogens (OEHHA, 2001a). The revised cancer potency derivation procedures described will not be used to impose any overall revisions of the existing cancer potencies, although they do reflect updated methods of derivation. However, individual cancer potency values will be reviewed as part of the ongoing re-evaluation of health values mandated by SB 25, and revised values will be listed in updated versions of the appendices to this document as necessary. The revisions also include the use of weighting factors in calculating cancer risks from exposures of infants, children and adolescents, to reflect their anticipated special sensitivity to carcinogens. Similar legal mandates to update risk assessment methodology and cancer potencies apply to the OEHHA program for development of Public Health Goals (PHGs) for chemicals in drinking water, and Proposition 65 No Significant Risk Levels (NSRLs). The NSRLs may also be revised to reflect concerns for children's health. Revising these numbers will require the originating program to reconsider the value in an open public process. For example, OEHHA would need to release any revised potency factors for public comment and review by the Scientific Review Panel on Toxic Air Contaminants (SRP) prior to adoption under the TAC program. The procedures for outside parties to request reevaluation of cancer potency values by the programs which originated those values are listed in Appendix G.

Appendices A and B provide previously adopted Cal/EPA values which were included in the previous version of the TSD for Cancer Potency Factors (OEHHA, 2005a). Cal/EPA values were developed under the Toxic Air Contaminant (TAC) program, the PHG program, the Proposition 65 program, or in some cases specifically for the Air Toxics Hot Spots program. All the Cal/EPA values are submitted for public comments and external peer review prior to adoption by the program of origin. In the future, new values developed by the Toxic Air

Contaminants or Hot Spots programs or other suitable sources will be added as these are approved.

Some U.S. EPA IRIS cancer unit risk values were adopted under the previous versions of these guidelines, and these values will continue to be used unless and until revised by Cal/EPA. U.S. EPA has recently revised its cancer risk assessment guidelines (U.S. EPA, 2005a). Some of the recommended changes in methodology could result in slightly different potency values compared to those calculated by the previous methodology, although in practice a number of the recommendations (for example, the use of ¾ power of the body weight ratio rather than ⅔ power for interspecies scaling) have been available in draft versions of the revised policy for some time and appear in many more recent assessments. U.S. EPA has stated that cancer potency values listed in IRIS will not be revisited solely for the purpose of incorporating changes in cancer potency value calculation methods contained in the revised cancer risk assessment guidelines. U.S. EPA has also issued supplementary guidelines on assessing cancer risk from early-life exposure (U.S. EPA, 2005b).

OEHHA uses a toxic equivalency factor procedure for dioxin-like compounds, including polychlorinated dibenzo-*p*-dioxins, dibenzofurans and polychlorinated biphenyls (PCBs). The Toxicity Equivalency Factor scheme (TEF_{WHO-97}) developed by the World Health Organization/European Center for Environmental Health (WHO-ECEH) is used for determining cancer unit risk and potency values for these chemicals where individual congener emissions are available (Appendix C).

This document is one part of the Air Toxics Hot Spots Program Risk Assessment Guidelines. The other documents originally included in the Guidelines are Part I: Technical Support Document for the Determination of Acute Toxicity Reference Exposure Levels for Airborne Toxicants; Part III: Technical Support Document for Determination of Noncancer Chronic Reference Exposure Levels; Part IV: Technical Support Document for Exposure Assessment and Stochastic Analysis; Part V: Air Toxic Hot Spots Program Risk Assessment Guidelines. As a part of the same revision process which led to production of this revised TSD on cancer potencies, the original TSDs for Acute and Chronic Reference Exposure Levels have been replaced with a new unified TSD for Acute, 8-hour and Chronic Reference Exposure Levels.

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Appendix A. A lookup table containing unit risk and cancer potency values.

Appendix B. Chemical-specific summaries of the information used to derive unit risk and cancer potency values.

Appendix C. A description of the use of toxicity equivalency factors for determining unit risk and cancer potency factors for polychlorinated dibenzo-*p*-dioxins, dibenzofurans and dioxin-like polychlorinated biphenyls.

Appendix D. A listing of Toxic Air Contaminants identified by the California Air Resources Board.

Appendix E. Descriptions of the International Agency for Research on Cancer (IARC) and U.S. Environmental Protection Agency (U.S. EPA) carcinogen classifications.

Appendix F. An asbestos quantity conversion factor for calculating asbestos concentrations expressed as 100 fibers/m^3 from asbestos concentrations expressed as $\mu g/m^3$.

Appendix G. Procedures for revisiting or delisting cancer potency factors by the program of origin.

Appendix H. Exposure routes and studies used to derive cancer unit risks and slope factors.

Appendix I. "Assessing susceptibility from early-life exposure to carcinogens": Barton *et al.*, 2005 (from *Environmental Health Perspectives).*

Appendix J. "In Utero and Early Life Susceptibility to Carcinogens: The Derivation of Age-at-Exposure Sensitivity Measures" – conducted by OEHHA's Reproductive and Cancer Hazard Assessment Branch.

Appendix K. Additions and corrections from prior document versions.

INTRODUCTION

The Technical Support Document (TSD) for Describing Available Cancer Potency Factors provides technical information support for the Air Toxics Hot Spots Program Risk Assessment Guidelines. The TSD consists of 12 sections:

1. The TSD introduction.
2. A description of the methodologies used to derive the unit risk and cancer potency values listed in the lookup table.
3. A lookup table containing unit risk and cancer potency values. (Appendix A)
4. Chemical-specific summaries of the information used to derive unit risk and cancer potency values. (Appendix B).
5. A description of the use of toxicity equivalency factors for determining unit risk and cancer potency factors for polychlorinated dibenzo-*p*-dioxins, dibenzofurans and dioxin-like polychlorinated biphenyls (Appendix C).
6. A listing of Toxic Air Contaminants identified by the California Air Resources Board (Appendix D).
7. Descriptions of the International Agency for Research on Cancer (IARC) and U.S. Environmental Protection Agency (U.S. EPA) carcinogen classifications (Appendix E).
8. An asbestos quantity conversion factor for calculating asbestos concentrations expressed as 100 fibers/m^3 from asbestos concentrations expressed as $\mu g/m^3$ (Appendix F).
9. Procedures for revisiting or delisting cancer potency factors by the program of origin (Appendix G).
10. Exposure routes and studies used to derive cancer unit risks and slope factors (Appendix H).
11. "Assessing susceptibility from early-life exposure to carcinogens": Barton *et al.*, 2005 (from *Environmental Health Perspectives)* (Appendix I).
12. "In Utero and Early Life Susceptibility to Carcinogens: The Derivation of Age-at-Exposure Sensitivity Measures" – conducted by OEHHA's Reproductive and Cancer Hazard Assessment Branch (Appendix J)

SELECTION OF CANCER POTENCY VALUES

The Office of Environmental Health Hazard Assessment (OEHHA) has developed a number of cancer potencies for use in the Toxic Air Contaminants and Air Toxics Hot Spots programs. This document also provides summaries of cancer potency factors which were originally developed for other California Environmental Protection Agency (Cal/EPA) programs, or by the U.S. EPA. These were reviewed for accuracy, reliance on up-to-date data and methodology, and applicability in the context of the Air Toxics Hot Spots program. Values found appropriate were adopted after public and peer review rather than devoting the resources necessary for a full *de novo* assessment. Thus, cancer potency values (CPF) included in the Technical Support Document (TSD) for Cancer Potency Factors were from the following sources:

1. Toxic Air Contaminant documents

2. Standard Proposition 65 documents

3. U.S.EPA Integrated Risk Information Systems (Office of Health and Environmental Assessment, U.S.EPA)

4. Expedited Proposition 65 documents

5. Other OEHHA assessments , for example for the drinking water program.

All the cancer potency value sources used generally follow the recommendations of the National Research Council on cancer risk assessment (NRC, 1983, 1994). All Cal/EPA program documents undergo a process of public comment and scientific peer review prior to adoption, although the procedures used vary according to the program. The publication procedure for Toxic Air Contaminant documents includes a public comment period and review by the Scientific Review Panel on Toxic Air Contaminants (SRP) before identification of a Toxic Air Contaminant by the Air Resources Board of the California Environmental Protection Agency (Cal/EPA). Furthermore, a petition procedure is available to initiate TAC document review and revision if appropriate because of new toxicity data. Documents developed for the Air Toxics Hot Spots program similarly undergo public comment and peer review by the SRP before adoption by the Director of OEHHA. The standard Proposition 65 document adoption procedure includes a public comment and external peer review by the Proposition 65 Carcinogen Identification Committee. The expedited Proposition 65 document adoption procedure included a public comment period. Risk assessments prepared for development of Public Health Goals (PHGs) for chemicals in drinking water are subject to two public comment periods before the final versions and responses to comments are published on the OEHHA Web site. PHG documents may also receive external peer review. Documents from U.S. EPA's Integrated Risk Information System (IRIS) receive external peer review and are posted on the Internet for public viewing during the external peer review period, and any public comments submitted are considered by the originating office. Additionally, public comment may be solicited during the document posting period. Future preference for use of developed cancer potency factors/unit risks will be done on a case by case basis. Preference will be given to those assessments most relevant to inhalation exposures of the California population, to the most recent derivations using the latest data sets and scientific methodology, and to those having undergone the most open and extensive peer review process.

CANCER RISK ASSESSMENT METHODOLOGIES

This section describes in general the methodologies used to derive the cancer unit risk and potency factors listed in this document. As noted in the Preface to this document, no new cancer unit risks or potency factors were developed for this document. All of the values contained here were previously developed in documents by Cal/EPA or U.S. EPA. Following the recommendations of the National Academy of Sciences (NRC, 1983), Cal/EPA and U.S. EPA have both used formalized cancer risk assessment guidelines, the original versions of which (California Department of Health Services, 1985; U.S. EPA, 1986) were published some time ago. Both these guidelines followed similar methodologies.

In the twenty years since these original guidelines were published there have been a number of advances in the methodology of cancer risk assessment. There have additionally been considerable advances in the quantity of data available not only from animal carcinogenesis bioassays and epidemiological studies, but also from mechanistic studies of carcinogenesis and related phenomena. Some of these advances have been incorporated into newer risk assessments by both agencies on a more or less *ad hoc* basis. There has also been an ongoing effort to provide updated risk assessment guidance documents. In 1995, U.S. EPA released for public comment the "Proposed and Interim Guidelines for Carcinogen Risk Assessment", which was the first of several drafts released for public comment. Many risk assessments appearing since then have used elements of the recommendations contained in that document, in spite of its draft status. A final version of the U.S. EPA's revised cancer risk assessment guidelines has now been released (U.S. EPA, 2005a). Although these new guidelines incorporate a number of substantial changes from their predecessors (U.S. EPA, 1986; 1995), U.S. EPA has stated that cancer potency values listed in IRIS will not be revisited solely for the purpose of incorporating changes in cancer potency value calculation methods.

Cal/EPA has not produced a revised cancer risk assessment guideline document to replace the original version (DHS, 1985). Rather, Cal/EPA has relied on incorporating new data and methodologies as these became available, and described the methods used on a case by case basis in the individual risk assessment documents where these went beyond the original guidance. However, this revision of the TSD for cancer potencies provides a convenient opportunity to summarize the current status of the methodology used by OEHHA for the air toxics programs, and also to highlight points of similarity to, and difference from, the recommendations of U.S. EPA (2005a).

In this document, OEHHA intends to follow the recommendations of the NRC (1994) in describing a set of clear and consistent principles for choosing and departing from default cancer risk assessment options. NRC identified a number of objectives that should be taken into account when considering principles for choosing and departing from default options. These include, "protecting the public health, ensuring scientific validity, minimizing serious errors in estimating risks, maximizing incentives for research, creating an orderly and predictable process, and fostering openness and trustworthiness". The OEHHA cancer risk methodologies discussed in this document are intended to generally meet those objectives cited above.

Hazard Identification

This section will describe: 1) how weight of evidence evaluations are used in hazard evaluation; 2) guidelines for inferring causality of effect; 3) the use of human and animal carcinogenicity data, as well as supporting evidence (e.g. genetic toxicity and mechanistic data); 4) examples of carcinogen identification schemes.

Evaluation of Weight of Evidence

In evaluating the range of evidence on the toxicity and carcinogenicity of a compound, mixture or other agent, a "weight-of-evidence" approach is generally used to describe the body of evidence on whether or not exposure to the agent causes a particular effect. Under this approach, the number and quality of toxicological and epidemiological studies, as well as the consistency of study results and other sources of data on biological plausibility, are considered. Diverse and sometimes conflicting data need to be evaluated with respect to possible explanations of differing results. Consideration of methodological issues in the review of the toxicological and epidemiological literature is important in evaluating associations between exposure to an agent and animal or human health effects. This aspect of the evaluation process has received particular emphasis with respect to epidemiological data, where concerns as to the statistical and biological significance and reliability of the data and the impacts of confounding and misclassification are pressing. Such concerns are also relevant to some extent in the interpretation of animal bioassay data and mechanistic studies. Although the test animals, laboratory environment and characterization of the test agent are usually much better controlled than the equivalent parameters in an epidemiological study, the small sample size can be problematic. In addition, there are uncertainties associated with extrapolation of biological responses from test animal species to humans.

Criteria for Causality

There has been extensive discussion over the last two centuries on causal inference. This has been particularly with regard to epidemiological data, but is also relevant to interpretation of animal studies. Most epidemiologists utilize causal inference guidelines based on those proposed by Bradford Hill (1971). OEHHA has relied on these and on recommendations by IARC (2006), the Institute of Medicine (2004), the Surgeon General's Reports on Smoking (U.S. DHHS, 2004) and standard epidemiologic texts (*e.g.* Lilienfeld and Lilienfeld, 1980; Rothman and Greenland, 1998). The criteria for determination of causality used by OEHHA have been laid out in various risk assessment documents. The summary below is adapted from the Health Effects section of the document prepared to support the identification of environmental tobacco smoke (ETS) as a Toxic Air Contaminant (OEHHA, 2005b).

1. *Strength of Association.* A statistically significant strong association, which is easier to detect if there is a high relative risk, between a factor and a disease is often viewed as an important criterion for inferring causality because, all other things being equal, a strong and statistically significant association makes alternative explanations for the disease less likely. However, as discussed in Rothman and Greenland (1998), the fact that a relative risk is small in magnitude does not exclude a casual association between the risk factor

and the outcome in question. Since it is more difficult to detect (i.e., reach statistical significance) a small magnitude risk, ~~they are~~it is just as likely to ~~be causal~~indicate causality as a larger magnitude risk~~s~~.

When assessing all evidence, it is important to consider the strength of the study design (particularly controlling for confounding variables, obtaining an unbiased sample, measurement error) and the level of statistical significance (i.e., the ability to exclude a Type I [false positive] error). The power of the study to detect biologically meaningful effects (i.e., the risk of a Type II [false negative] error) is important in considering studies that do not reach traditional (i.e., $P<.05$) statistical significance, particularly if the biological endpoint is serious. If the outcome is serious and the study small (i.e., low power), a larger P value (e.g., $P<.10$) may be adequate evidence for identifying an effect.

There are a number of examples of statistically significant, small magnitude associations that are widely accepted as causal, such as causal links between air pollution and cardiovascular/pulmonary mortality and between second-hand smoke exposure and various cancers and heart disease. From a public health perspective, even a small magnitude increase in risk for a common disease can mean large numbers of people affected by the health outcome when exposure is frequent and widespread, as measured by the population attributable risk or attributable fraction. Small magnitude of association must not be confused with statistical significance, which is much more important.

2. *Consistency of Association.* If several investigations find an association between a factor and a disease across a range of populations, geographic locations, times, and under different circumstances, then the factor is more likely to be causal. Consistency argues against hypotheses that the association is caused by some other factor(s) that varies across studies. Unmeasured confounding is an unlikely explanation when the effect is observed consistently across a number of studies in different populations.

   Associations that are replicated in several studies of the same design or using different epidemiological approaches or considering different sources of exposure and in a number of geographical regions are more likely to represent a causal relationship than isolated observations from single studies (IARC, 2006). If there are inconsistent results among investigations, possible reasons are sought, such as adequacy of sample size or control group, methods used to assess exposure, or range in levels of exposure. The results of studies judged to be rigorous are emphasized over those of studies judged to be methodologically less rigorous. For example, studies with the best exposure assessment are more informative for assessing the association between ETS and breast cancer than studies with limited exposure assessment, all else being equal.

3. *Temporality.* Temporality means that the factor associated with causing the disease occurs in time prior to development of the disease. The adverse health effect should occur at a time following exposure that is consistent with the nature of the effect. For example, respiratory irritation immediately following exposure to an irritant vapor is temporally consistent, whereas ~~effects~~ irritation noted only years later may not be. On the other hand, tumors, noted immediately following exposure, might be temporally

inconsistent with a causal relationship, but tumors arising after a latency period of months (in rodents) or years (in rodents or humans) would be temporally consistent.

4. *Coherence and Biological Plausibility.* A causal interpretation cannot conflict with what is known about the biology of the disease. The availability of experimental data or mechanistic theories consistent with epidemiological observations strengthens conclusions of causation. For example, the presence of known carcinogens in tobacco smoke supports the concept that exposure to tobacco smoke could cause increased cancer risk. Similarly, if the mechanism of action for a toxicant is consistent with development of a specific disease, then coherence and biological plausibility can be invoked. It should be noted that our understanding of the biology of disease, and therefore biological plausibility, changes in light of new information which is constantly emerging from molecular biology (including epigenetics), and from new clinical and epidemiological investigations revealing effects influenced by genetic polymorphisms, pre-existing disease, and so forth.

5. *Dose-Response.* A basic tenet of toxicology is that increasing exposure or dose generally increases the response to the toxicant. While dose-response curves vary in shape and are not necessarily always monotonic, an increased gradient of response with increased exposure makes it difficult to argue that the factor is not associated with the disease. To argue otherwise necessitates that an unknown factor varies consistently with the dose of the substance and the response under question. While increased risk with increasing levels of exposure is considered to be a strong indication of causality, absence of a graded response does not exclude a causal relationship (IARC, 2006).

   The dose-response curves for specific toxic effects may be non-monotonic. Under appropriate circumstances, where the dose response shows saturation, the effect of exposures could be nearly maximal, with any additional exposure having little or no effect. In some instances, a response is seen strongly in susceptible subpopulations, and the dose-response is masked by mixing susceptible and non-susceptible individuals in a sample. Further, there are examples of U-shaped or inverted U-shaped dose-response curves, (e.g., for endocrine disrupters) (Almstrup et al., 2002; Lehmann et al., 2004). Finally, timing of exposure during development may mask an overall increase in risk with increasing dose.

6. *Specificity.* Specificity is generally interpreted to mean that a single cause is associated with a single effect. It may be useful for determining which microorganism is responsible for a particular disease, or associating a single carcinogenic chemical with a rare and characteristic tumor (e.g., liver angiosarcoma and vinyl chloride, or mesothelioma and asbestos). However, the concept of specificity is not helpful when studying diseases that are multifactorial, or toxic substances that contain a number of individual constituents, each of which may have several effects and/or target sites.

7. *Experimental evidence.* While experiments are often conducted over a short period of time or under artificial conditions (compared to real-life exposures), experiments offer the opportunity to collect data under highly controlled conditions that allow strong causal conclusions to be drawn. Experimental data that are consistent with epidemiological

results strongly support conclusions of causality. There are also "natural experiments" that can be studied with epidemiological methods, such as when exposure of a human population to a substance declines or ceases; if the effect attributed to that exposure decreases, then there is evidence of causality. One example of this is the drop in heart disease death and lung cancer risk after smoking cessation.

It should be noted that the causal criteria are guidelines for judging whether a causal association exists between a factor and a disease, rather than hard-and-fast rules. Lilienfeld and Lilienfeld (1980) note that "*In medicine and public health, it would appear reasonable to adopt a pragmatic concept of causality. A causal relationship would be recognized to exist whenever evidence indicates that the factors form part of the complex of circumstances that increases the probability of the occurrence of disease and that a diminution of one or more of these factors decreases the frequency of that disease. After all, the reason for determining the etiological factors of a disease is to apply this knowledge to prevent the disease.*" Rothman and Greenland (2005) discuss the complexities of causation and the use of rules and deductive methods in causal inference. They also concur with Bradford Hill and others that a determination of causality is a pragmatic conclusion rather than an absolute verdict, and advocate that these criteria should be seen as "*deductive tests of causal hypotheses*".

Data sources

Human studies: epidemiology, ecological studies and case reports

The aim of a risk assessment for the California Air Toxics programs is to determine potential impact on human health. Ideally therefore, the hazard identification would rely on studies in humans to demonstrate the nature and extent of the hazard. However, apart from clinical trials of drugs, experimental studies of toxic effects in human subjects are rarely undertaken or justifiable. Pharmacokinetic studies using doses below the threshold for any toxic effect have been undertaken for various environmental and occupational agents, but are not usually regarded as appropriate for suspected carcinogens.

The human data on carcinogens available to the risk assessor therefore mostly consist of epidemiological studies of existing occupational or environmental exposures. It is easier to draw reliable inferences in situations where both the exposures and the population are substantial and well-defined, and accessible to direct measurement rather than recall. Thus, many important findings of carcinogenicity to humans are based on analysis of occupational exposures. Problems in interpretation of occupational epidemiological data include simultaneous exposure to several different known or suspected carcinogens, imprecise quantification of exposures and confounding exposures such as active or passive tobacco smoking. The historical database of occupational data has a bias towards healthy white adult males. Thus, the hazard analysis of these studies may not accurately characterize effects on women, infants, children or the elderly, or on members of minority ethnic groups. Nevertheless, the analysis of occupational epidemiological studies, including meta-analyses, has proved an important source for unequivocal identification of human carcinogens.

Epidemiological evidence may also be obtained where a substantial segment of a general population is exposed to the material of interest in air, drinking water or food sources. Rigorous

cohort and case-control studies may sometimes be possible, in which exposed individuals are identified, their exposure and morbidity or mortality evaluated, and compared to less exposed but otherwise similar controls. More often at least the initial investigation is a cross-sectional study, where prevalence of exposures and outcomes is compared in relatively unexposed and exposed populations. Such studies are hypothesis-generating, but are important sources of information nevertheless, and can often also justify more costly and labor-intensive follow-up cohort and/or case-control studies.

The clinical medical literature contains many case reports where a particular health outcome is reported along with unusual exposures that might have contributed to its occurrence. These reports typically describe a single patient or a small group, and have no statistical significance. They are nevertheless useful as indications of possible associations that deserve follow-up using epidemiological methods, and as supporting evidence, addressing the plausibility of associations measured in larger studies.

Animal studies

Although the observation of human disease in an exposed population can provide definitive hazard identification, adequate data of this type are not always available. More often, risk estimates have to be based on studies in experimental animals, and extrapolation of these results to predict human toxicity. The animals used are mostly rodents, typically the common laboratory strains of rat and mouse.

Rats and mice have many similarities to humans. Physiology and biochemistry are similar for all mammals, especially at the fundamental levels of xenobiotic metabolism, DNA replication and DNA repair that are of concern in identifying carcinogens. However, there are also several important differences between rodents and humans. Rodents, with a short life span, have differences in cell growth regulation compared to longer-lived species such as the human. For instance, whereas laboratory investigations have suggested that mutations in two regulatory genes (*e.g.* H-ras and p-53) are sometimes sufficient to convert a rodent cell to a tumorigenic state, many human cancers observed clinically have seven or eight such mutations. In addition, cultured normal human cells have a very stable karyotype, whereas cultured rodent cells facilely undergo tetraploidization and then aneuploidization in cell culture. Further, cultured human cells senesce and rarely undergo spontaneous immortalization (frequency is 10^{-7} or less), whereas cultured rodent cells facilely undergo immortalization at frequencies on the order of 10^{-3}. The use of genomics to study chemical carcinogenesis is relatively new, but the differences at present appear to be a matter of degree rather than kind.

Differences in regulation of cell division are another likely reason for variation between species in the site of action of a carcinogen, or its potency at a particular site. A finding of carcinogenesis in the mouse liver, for instance, is a reasonably good indicator of potential for carcinogenesis at some site in the human, but not usually in human liver (Huff, 1999). The mouse liver (and to a lesser extent that of the rat) is a common site of spontaneous tumors. It is also relatively sensitive to chemical carcinogenesis. The human liver is apparently more resistant to carcinogenesis; human liver tumors are unusual except when associated with additional predisposing disease, such as hepatitis B or alcoholic cirrhosis, or exposure to aflatoxin B1, or simultaneous exposure to hepatitis B virus and aflatoxin B1. Conversely, other

tumor sites are more sensitive in the human than in experimental animals. Interspecies variation in site and sensitivity to carcinogenesis may also arise from differences in pharmacokinetics and metabolism, especially for carcinogens where metabolic activation or detoxification is important. This variability may cause important differences in sensitivity between individuals in a diverse population such as humans. Variability between individuals in both susceptibility and pharmacokinetics or metabolism is probably less in experimental animal strains that are bred for genetic homogeneity.

Animal carcinogenesis studies are often designed to maximize the chances of detecting a positive effect, and do not necessarily mimic realistic human exposure scenarios. Thus extrapolation from an experimentally accessible route to that of interest for a risk assessment may be necessary. Even for studies by realistic routes such as oral or inhalation, doses may be large compared to those commonly encountered in the environment, in order to counter the limitation in statistical power caused by the relatively small size of an animal experiment. Whereas the exposed population of an epidemiological study might number in the thousands, a typical animal study might have fifty individuals per exposure group. With this group size any phenomenon with an incidence of less than about 5% is likely to be undetectable. Statistically significant results may be obtained even with groups as small as ten animals per dose group, when incidence of a tumor that is rare in the controls approached 100% in a treated group. The consensus experimental design for animal carcinogenesis studies, which has evolved over the last 50 years of investigation, is represented by the protocol used by the U.S. National Toxicology Program (NTP) for studies using oral routes (diet, gavage or drinking water) or inhalation. These carcinogenesis bioassays usually involve both sexes of an experimental species, and most often two species. NTP has standardized the use of the C57BlxC3H F_1 hybrid mouse, and the Fischer 344 rat as the standard test species, although NTP has announced plans to substitute use of the Wistar Han rat for the Fisher 344 rat. There is now an extensive database of background tumor incidences, normal physiology, biochemistry, histology and anatomy for these strains, which aids in the interpretation of pathological changes observed in experiments. Nevertheless, there is enough variation in background rates of common tumors that the use of concurrent controls is essential for hazard identification or dose-response assessment. "Historical control" data are mainly used to reveal anomalous outcomes in the concurrent controls. The fact that a significantly elevated incidence of a tumor relative to the concurrent control group is within the range of historical controls at that site for the test sex and strain is not necessarily grounds for dismissing the biological significance of the finding.

Groups of fifty animals of each sex and species are used, with control groups, and several dose groups, the highest receiving the maximum tolerated dose (MTD). Recent study designs have emphasized the desirability of at least three dose levels covering a decade with "logarithmic" spacing (*i.e.* MTD, 1/2 MTD or 1/3 MTD, and 1/10 MTD). This extended design is aimed at providing better dose-response information, and may contribute important additional information, such as mechanistic insights, for the hazard identification phase.

Supporting evidence: genetic toxicity, mechanistic studies

Investigators have developed additional data sources that can support or modify the conclusions of animal carcinogenesis bioassays, and provide information on mechanisms of action of agents suspected of being carcinogenic based on epidemiological studies or animal bioassays.

Genetic damage in exposed organisms includes both gene mutations (point or frameshift), and larger scale effects such as deletions, gene amplification, sister-chromatid exchanges, translocations and loss or duplication of segments or whole chromosomes. These genetic effects of chemical exposures are deleterious in their own right. In addition, since carcinogenesis results from somatic mutations and similar genetic alterations, agents that cause genetic damage generally have carcinogenic potential. Conversely, many known carcinogens are also known to be genotoxic, although there is also a significant class of carcinogens that are not directly genotoxic according to the usual tests. These latter agents presumably work by some other mechanism, such as methylation of tumor suppressor genes or demethylation of cellular proto-oncogenes, although recent genetic studies have shown that even tumors induced by these agents may show mutations, deletions or amplification of growth regulatory genes.

Experimental procedures to demonstrate and measure genetic toxicity may involve exposure of intact animals, and examination of genetic changes in, for example, bone marrow cells (or cells descended from these e.g. the micronucleus test, which detects remnants of chromosomal fragments in immature erythrocytes), mutations in flies (*Drosophila)*, or appearance of color spots in the coat of mice. However, many tests have employed single celled organisms or mammalian cells in culture. The best known of these tests is the *Salmonella* reverse mutation assay, popularly known as the Ames test after its inventor. This is representative of a larger class of tests for mutagenic activity in prokaryotic organisms (bacteria), which necessarily only look at gene-level mutations. Similar tests in eukaryotic microorganisms (yeasts, *Aspergillus*) and cultured mammalian cells also detect chromosomal effects. Many tests using microorganisms *in vitro* involve addition of activating enzymes (*e.g.* liver postmitochondrial supernatant – "S9") to mimic the metabolism of promutagenic chemicals *in vivo*. Another type of test examines the induction in mammalian cells of morphological transformation or anchorage-independent growth. These two chemically induced, *in vitro* changes are considered two of the many changes that fibroblastic cells must undergo on their route to neoplastic transformation (tumorigenicity). These various genetic tests contribute different information, which may be used to amplify and confirm conclusions drawn from human studies or animal bioassays, or to draw conclusions in the absence of epidemiological or bioassay data. In the latter case they have also been used in prioritizing agents for further evaluation by means of bioassays.

Carcinogen Identification schemes

Some regulatory programs, such as California's Safe Drinking Water and Toxics Enforcement Act ("Proposition 65") and various activities of the U.S. EPA, require that explicit lists of substances having the potential to act as human carcinogens be maintained. Other such lists are developed by non-regulatory research organizations, such as the U.S. National Toxicology Program and the International Agency for Research on Cancer (IARC), an international program of the World Health Organization. The California air toxics programs do not have any statutory requirement to "identify" carcinogens. The requirement instead is to identify hazardous substances as Toxic Air Contaminants, and to determine whether or not a threshold concentration, below which no adverse effects are expected, is likely to exist:

HEALTH AND SAFETY CODE, Division 26 (Air Resources), § 39660..

(2) The evaluation shall also contain an estimate of the levels of exposure that may cause or contribute to adverse health effects. If it can be established that a threshold of adverse health effects exists, the estimate shall include both of the following factors:

(A) The exposure level below which no adverse health effects are anticipated.

(B) An ample margin of safety that accounts for the variable effects that heterogeneous human populations exposed to the substance under evaluation may experience, the uncertainties associated with the applicability of the data to human beings, and the completeness and quality of the information available on potential human exposure to the substance. In cases in which there is no threshold of significant adverse health effects, the office shall determine the range of risk to humans resulting from current or anticipated exposure to the substance.

In practice however this requirement amounts to the need to establish whether or not a substance is carcinogenic. Any such effects are clearly harmful. Whereas the great majority of non-cancer health effects of chemicals are regarded as having a threshold, the default assumption for carcinogens is that there is no threshold (as described below). OEHHA follows the guidelines laid out by IARC for identification and classification of potential human carcinogens, which are described in detail in the most recent revision of the *Preamble* to the IARC monographs series (IARC, 2006). The IARC Monograph series provides evaluations of the carcinogenicity of individual substances or commonly occurring mixtures. The evaluation guidelines used are similar to those used by other scientific or regulatory authorities, including U.S.EPA.

The data inputs to hazard identification for carcinogens are human epidemiological studies, animal bioassays, along with supporting evidence such as mechanistic and genotoxicity data and structure-activity comparisons. IARC also assembles data on the structure and identity of the agent. The list of agents considered includes specific chemicals and also complex mixtures, occupational and lifestyle factors, physical and biological agents, and other potentially carcinogenic exposures.

IARC evaluations determine the quality of evidence for both animal and human evidence as falling into one of four categories: sufficient evidence of carcinogenicity, limited evidence of carcinogenicity, inadequate evidence of carcinogenicity and evidence suggesting lack of carcinogenicity. Stringent requirements for data quality are imposed. In view of their crucial importance, these definitions are quoted directly from the *Preamble* (IARC 2006):

"(a) Carcinogenicity in humans

Sufficient evidence of carcinogenicity: The Working Group considers that a causal relationship has been established between exposure to the agent and human cancer. That is, a positive relationship has been observed between the exposure and cancer in studies in which chance, bias and confounding could be ruled out with reasonable confidence. A statement that there is *sufficient evidence* is followed by a separate sentence that identifies the target organ(s) or tissue(s) where an increased risk of cancer was observed in humans. Identification of a specific target organ or tissue does not preclude the possibility that the agent may cause cancer at other sites.

Limited evidence of carcinogenicity: A positive association has been observed between exposure to the agent and cancer for which a causal interpretation is considered by the Working Group to be credible, but chance, bias or confounding could not be ruled out with reasonable confidence.

Inadequate evidence of carcinogenicity: The available studies are of insufficient quality, consistency or statistical power to permit a conclusion regarding the presence or absence of a causal association between exposure and cancer, or no data on cancer in humans are available.

Evidence suggesting lack of carcinogenicity: There are several adequate studies covering the full range of levels of exposure that humans are known to encounter, which are mutually consistent in not showing a positive association between exposure to the agent and any studied cancer at any observed level of exposure. The results from these studies alone or combined should have narrow confidence intervals with an upper limit close to the null value (e.g. a relative risk of 1.0). Bias and confounding should be ruled out with reasonable confidence, and the studies should have an adequate length of follow-up. A conclusion of *evidence suggesting lack of carcinogenicity* is inevitably limited to the cancer sites, conditions and levels of exposure, and length of observation covered by the available studies. In addition, the possibility of a very small risk at the levels of exposure studied can never be excluded.

(b) Carcinogenicity in experimental animals

Carcinogenicity in experimental animals can be evaluated using conventional bioassays, bioassays that employ genetically modified animals, and other in-vivo bioassays that focus on one or more of the critical stages of carcinogenesis. In the absence of data from conventional long-term bioassays or from assays with neoplasia as the end-point, consistently positive results in several models that address several stages in the multistage process of carcinogenesis should be considered in evaluating the degree of evidence of carcinogenicity in experimental animals.

The evidence relevant to carcinogenicity in experimental animals is classified into one of the following categories:

Sufficient evidence of carcinogenicity: The Working Group considers that a causal relationship has been established between the agent and an increased incidence of malignant neoplasms or of an appropriate combination of benign and malignant neoplasms in (a) two or more species of animals or (b) two or more independent studies in one species carried out at different times or in different laboratories or under different protocols. An increased incidence of tumours in both sexes of a single species in a well-conducted study, ideally conducted under Good Laboratory Practices, can also provide *sufficient evidence*.

A single study in one species and sex might be considered to provide *sufficient evidence of carcinogenicity* when malignant neoplasms occur to an unusual degree with regard to incidence, site, type of tumour or age at onset, or when there are strong findings of tumours at multiple sites.

Limited evidence of carcinogenicity: The data suggest a carcinogenic effect but are limited for making a definitive evaluation because, e.g. (a) the evidence of carcinogenicity is

restricted to a single experiment; (b) there are unresolved questions regarding the adequacy of the design, conduct or interpretation of the studies; (c) the agent increases the incidence only of benign neoplasms or lesions of uncertain neoplastic potential; or (d) the evidence of carcinogenicity is restricted to studies that demonstrate only promoting activity in a narrow range of tissues or organs.

***Inadequate evidence of carcinogenicity*:** The studies cannot be interpreted as showing either the presence or absence of a carcinogenic effect because of major qualitative or quantitative limitations, or no data on cancer in experimental animals are available.

***Evidence suggesting lack of carcinogenicity*:** Adequate studies involving at least two species are available which show that, within the limits of the tests used, the agent is not carcinogenic. A conclusion of *evidence suggesting lack of carcinogenicity* is inevitably limited to the species, tumour sites, age at exposure, and conditions and levels of exposure studied."

IARC utilizes the evaluations of animal and human data, along with supporting evidence including genotoxicity, structure-activity relationships, and identified mechanisms, to reach an overall evaluation of the potential for carcinogenicity in humans. The revised *Preamble* (IARC, 2006) includes a description of the data evaluation criteria for this supporting evidence, and indications as to the situations where the availability of supporting evidence may be used to modify the overall conclusion from that which would be reached on the basis of bioassay and/or epidemiological evidence alone. The overall evaluation is expressed as a numerical grouping, the categories of which are described below, as before by directly quoting IARC (2006):

"Group 1: The agent is *carcinogenic to humans*.

This category is used when there is *sufficient evidence of carcinogenicity* in humans. Exceptionally, an agent may be placed in this category when evidence of carcinogenicity in humans is less than *sufficient* but there is *sufficient evidence of carcinogenicity* in experimental animals and strong evidence in exposed humans that the agent acts through a relevant mechanism of carcinogenicity.

Group 2.

This category includes agents for which, at one extreme, the degree of evidence of carcinogenicity in humans is almost *sufficient*, as well as those for which, at the other extreme, there are no human data but for which there is evidence of carcinogenicity in experimental animals. Agents are assigned to either Group 2A (*probably carcinogenic to humans*) or Group 2B (*possibly carcinogenic to humans*) on the basis of epidemiological and experimental evidence of carcinogenicity and mechanistic and other relevant data. The terms *probably carcinogenic* and *possibly carcinogenic* have no quantitative significance and are used simply as descriptors of different levels of evidence of human carcinogenicity, with *probably carcinogenic* signifying a higher level of evidence than *possibly carcinogenic*.

Group 2A: The agent is *probably carcinogenic to humans*.

This category is used when there is *limited evidence of carcinogenicity* in humans and *sufficient evidence of carcinogenicity* in experimental animals. In some cases, an agent may be classified in this category when there is *inadequate evidence of carcinogenicity* in humans and *sufficient evidence of carcinogenicity* in experimental animals and strong evidence that the carcinogenesis is mediated by a mechanism that also operates in humans. Exceptionally, an agent may be classified in this category solely on the basis of *limited evidence of carcinogenicity* in humans. An agent may be assigned to this category if it clearly belongs, based on mechanistic considerations, to a class of agents for which one or more members have been classified in Group 1 or Group 2A.

Group 2B: The agent is *possibly carcinogenic to humans.*

This category is used for agents for which there is *limited evidence of carcinogenicity* in humans and less than *sufficient evidence of carcinogenicity* in experimental animals. It may also be used when there is *inadequate evidence of carcinogenicity* in humans but there is *sufficient evidence of carcinogenicity* in experimental animals. In some instances, an agent for which there is *inadequate evidence of carcinogenicity* in humans and less than *sufficient evidence of carcinogenicity* in experimental animals together with supporting evidence from mechanistic and other relevant data may be placed in this group. An agent may be classified in this category solely on the basis of strong evidence from mechanistic and other relevant data.

Group 3: The agent is *not classifiable as to its carcinogenicity to humans.*

This category is used most commonly for agents for which the evidence of carcinogenicity is *inadequate* in humans and *inadequate* or *limited* in experimental animals.

Exceptionally, agents for which the evidence of carcinogenicity is *inadequate* in humans but *sufficient* in experimental animals may be placed in this category when there is strong evidence that the mechanism of carcinogenicity in experimental animals does not operate in humans.

Agents that do not fall into any other group are also placed in this category.

An evaluation in Group 3 is not a determination of non-carcinogenicity or overall safety. It often means that further research is needed, especially when exposures are widespread or the cancer data are consistent with differing interpretations.

Group 4: The agent is *probably not carcinogenic to humans.*

This category is used for agents for which there is *evidence suggesting lack of carcinogenicity* in humans and in experimental animals. In some instances, agents for which there is *inadequate evidence of carcinogenicity* in humans but *evidence suggesting lack of carcinogenicity* in experimental animals, consistently and strongly supported by a broad range of mechanistic and other relevant data, may be classified in this group."

The IARC hazard evaluation system provides a detailed and generally accepted scheme to classify the strength of evidence as to the possible human carcinogenicity of chemicals and other agents. This includes careful consideration of mechanistic data and other supporting evidence, the evaluation of which is also important to inform selection of models or defaults used in dose response assessment, as is described below. The extended consideration of supporting evidence is in fact the primary difference between more recent versions of the guidance from IARC, and also by other organizations including U.S. EPA, and the original versions of that guidance. In fact, the basic criteria for hazard identification based on bioassay and epidemiological data have not changed substantially in other respects from earlier guidance documents, including that originally published by California (DHS, 1985). Although as noted earlier the California Air Toxics programs do not categorize identified carcinogens, it has generally been the practice to regard any agent with an IARC overall classification in Group 1 or Group 2 as a known or potential human carcinogen. This implies the selection of various policy-based default options, including absence of a threshold in the dose-response curve, unless specific data are available to indicate otherwise. The same basic identification criteria are used by OEHHA scientific staff to determine the appropriate treatment of agents not evaluated by IARC, or for which newer data or revised interpretations suggest that an earlier IARC determination is no longer appropriate.

U.S. EPA has also proposed a scheme for carcinogen hazard identification and strength of evidence classification in their recently finalized Guidelines for Carcinogen Risk Assessment (U.S. EPA, 2005). These principally differ from the IARC guidance in recommending a more extensive narrative description rather than simply a numerical identifier for the identified level of evidence, and also to some degree in the weight accorded to various types of supporting evidence. However, for most purposes they may be regarded as broadly equivalent to the scheme used by IARC, and OEHHA has chosen to cite the IARC (2006) *Preamble* as representing the most up-to-date and generally accepted guidance on this issue.

Dose Response Assessment

The dose-response phase of a cancer risk assessment aims to characterize the relationship between an applied dose of a carcinogen and the risk of tumor appearance in a human. This is usually expressed as a cancer slope factor ["potency" – in units of reciprocal dose - usually $(mg/kg\text{-}body\ weight.day)^{-1}$ or "unit risk" – reciprocal air concentration – usually $(\mu g/m^3)^{-1}$] for the lifetime tumor risk associated with lifetime continuous exposure to the carcinogen at low doses. Cancer potency factors may also be referred to as "cancer slope factors". (As will be described later, additional algorithms may need to be applied to determine risk for specific age groups, or at higher doses where toxicokinetic factors have significant effect.) The basic methodologies recommended in this document are similar to those described by U.S. EPA (2005a) in their Carcinogen Risk Assessment Guidelines. This document therefore refers to U.S. EPA (2005a) for explanation of detailed procedures, and will provide only a brief summary except in cases where OEHHA recommendations are different from or more explicit than those of U.S. EPA.

The following descriptions of methods for dose response assessment, and considerations in their application, apply in principle to the analysis of both animal and human (epidemiological) cancer incidence data. Indeed, the original formulation of the multistage model (Armitage and Doll, 1954) described below was developed based on human cancer incidence. Nevertheless, the

number and quality of human cancer incidence datasets is limited. The more complex analyses have usually only been possible for animal experimental data, where the interindividual variability and the exposure conditions can be both measured and controlled. Most commonly, epidemiological studies have necessarily used a form of multivariate analysis to separate the effects of several different variables relating to exposure, demographics and behaviors (e.g. smoking). In these analyses it is usually assumed that the effect measure(s) vary linearly with the exposure: any more complex variance assumptions might exceed the power of the data to determine the required model parameters. However, there are exceptions, especially for occupational studies where the critical exposure is measured as a continuous variable (rather than just categorical) and where the effect of this exposure is substantial relative to other confounding factors. For example, OEHHA (1998) used a multistage model dealing with both exposure intensity and duration in the analysis of cancer incidence in railroad workers exposure to diesel exhaust (Garshick et al., 1988)

Interspecies Extrapolation

The procedures used to extrapolate low-dose human cancer risk from epidemiological or animal carcinogenicity data are generally health-protective in that they determine an upper confidence bound on the risk experienced by an exposed population. As statistical estimates they cannot be regarded as definite predictions of the risk faced by any one specific individual, who might for a variety of reasons, including individual exposure and susceptibility, experience a risk different from the estimate. The risk assessment procedures used aim to include the majority of variability in the general human population within the confidence bound of the estimate, although the possibility that some individuals might experience either lower or even no risk, or a considerably higher risk, cannot be excluded. Additionally, differences may exist between the characteristics of the general public and those of studied populations. For example, healthy workers, the subject of most epidemiological studies, are often found to have lower rates of morbidity and mortality than the general population (Wen et al., 1983; Monson, 1986; Rothman and Greenland, 1998). Most human data are derived from studies of largely male adult workers and risk estimates cannot take into account specific physiological factors of women, children, and older populations that may affect the potency of a carcinogen, including early age-at-exposure.

Dose-response assessment based on environmental epidemiological studies may involve evaluation of health impacts at exposure levels within the range of those measured in the study population. However, more usually the source data are studies of occupationally exposed humans or of animals, in which case the exposures in the study are likely to be much higher than those of concern for risk assessments relating to community or ambient exposures. Further, even when extrapolation from animal species to humans is not required, the general population to which the URF is applied may differ in characteristics relative to the occupational population studied. It is therefore necessary to extrapolate from the available data to the population and exposure range of concern, which is done by using a dose-response model derived from the source data. The models used fall into three main classes; mechanistically based models, empirical models and (where data are lacking to support a true data-based model) default assumptions. The factors affecting the dose-response relationships for carcinogenesis may also be divided into those relating to absorption, distribution, metabolism and excretion on the one hand (*i.e.* toxicokinetics), and those relating to the underlying dose-response characteristics of carcinogenesis at the tissue or cellular level (*i.e.* toxicodynamics). In this sense the problem of

dose response assessment for carcinogens is similar to that for non-cancer toxic effects. The toxicokinetic models used may in fact be similar for both situations, but the toxicodynamic models are generally different.

Intraspecies Extrapolation and Inter-individual Variability

In estimating the impact of a particular level of exposure to a carcinogen on a target human population, it is necessary to consider the range of susceptibility in the target population. In the present case this is typically defined as the general population of the State of California, including of course women (some of whom are pregnant), infants and children, the elderly, the sick, and those with genetic polymorphisms or acquired differences which affect their susceptibility to carcinogens. In general it has been assumed that the upper-bound risk estimates obtained from the standard toxicodynamic models described below are sufficiently health-protective to cover the intrinsic variability of the adult human target population, in spite of the fact that these models do not explicitly address this type of variability, except in the few cases where an estimate is based on epidemiological data from a large and unselected study group (U.S. EPA, 2005a). However, various analyses (Drew et al., 1983; Barton et al., 2005; Appendix J) have suggested that this assumption is inadequate to cover the expected variability within a human population that includes infants and children. Accordingly both U.S. EPA (2005b) and this document ~~(page 30 *et seq.*)~~ now offer guidance on the use of age-specific adjustment factors to allow for the potentially greater sensitivity of infants and children to chemical carcinogenesis.

The ability to accommodate human variability with regard to the toxicokinetic factors affecting susceptibility to carcinogens varies with the level of detail used in the particular assessment. If the generic interspecies extrapolation approach based on body weight is used without any explicit toxicokinetic model then the assumption is made, as in the case of toxicodynamic variability, that the overall health-protective assumptions made are sufficient to cover the toxicokinetic variability. On the other hand if explicit models such as those referenced in the following paragraph are used, this variability may be more explicitly accommodated by using parameter values which are taken as point estimates from measured distributions of population values, or by using Monte Carlo techniques to include those distributions in the model (Bois et al., 1996; OEHHA, 1992; 2001b).

Toxicokinetic Models

Considerable literature exists showing the importance of understanding the toxicokinetics of carcinogens in understanding their mechanism of action, sites of impact and dose-response relationships. U.S. EPA (2005) in Section 3.1 refers to the importance of identifying an appropriate dose metric for the dose-response analysis. Early cancer risk assessments typically used applied dose as the dose metric, which is adequate in simple cases provided appropriate correction factors are applied for interspecies extrapolation. However, it is often observed that the uptake, metabolism and elimination of the carcinogenic substance (and/or a procarcinogen and metabolites) is non-linear, especially at the higher doses employed in experimental animal studies (Hoel *et al.*, 1983, Gaylor *et al.*, 1994). Extrapolation to lower doses where such relationships tend to linearity (Hattis, 1990) is aided by the use of toxicokinetic models. These may be relatively simple compartment models, or sophisticated "physiologically based pharmacokinetic (PBPK) models" which to a greater or lesser degree model the actual

biochemical and physiological events of toxicokinetic importance. Applications of both types of model may be found in various risk assessment documents prepared for the Toxic Air Contaminants program (and other OEHHA risk assessments). Since the details vary widely according to the nature of the chemical and the availability of appropriate kinetic data these general guidelines will defer to those examples rather than attempt a fuller exposition here. Further analysis of the use of toxicokinetic modeling in extrapolation from animals to humans, and in accounting for interindividual variability among adult humans, infants and children is presented in the Air Toxics Hot Spots *Technical Support Document for the Derivation of Noncancer Reference Exposure Levels* (OEHHA, ~~2007: Public Review Draft~~2008). Although this refers to the use of toxicokinetic modeling in non-cancer risk assessment, the primary considerations are similar for cancer risk assessment.

Toxicodynamic Models

An early use of mechanistic analysis to support risk assessment was the development of the Armitage-Doll multistage model of dose-response for carcinogenesis. The multistage model was initially developed on theoretical grounds, and by examination of epidemiological and animal data on time to tumor incidence. Subsequent discovery of the molecular biology of proto-oncogenes has provided a basis for explaining the model in terms of actual biological events and systems (Barrett and Wiseman, 1987). This model was developed by Crump and others into the "linearized multistage model", which has been extensively used for carcinogen risk assessment. It leads to a number of partially verifiable predictions, including linearity of the dose-response relationship at low doses, which is observed for many genotoxic carcinogens. It also predicts the form of the dose-response relationship at higher doses, which generally follow a polynomial form (subject to sampling and background corrections) except where other identifiable factors such as pharmacokinetics intervene.

It has been argued that the simple linearized form of the multistage model has limitations as a description of carcinogenic mechanisms, which detract from its usefulness and generality. Cell proliferation is known to be important in the progression of cancer. It may actually be the primary mechanism of action for a few carcinogens, as opposed to the direct modification of DNA by the carcinogen or a metabolite which is assumed to cause the mutational event at each stage in the original multistage description. A cell proliferation model has been developed (Moolgavkar and Knudson, 1981), which retains the concept of an initiating mutational event (in most cases caused by interaction of the chemical with DNA, although it could also be a spontaneous mutation) as in the original multistage model, but also considers proliferation, death or terminal differentiation of both normal and initiated cells. This model is thought to better describe the biological events in carcinogenesis. However, it has not been used extensively in risk assessment because it requires many parameters that are difficult to define and measure (such as proliferation and death rates for various classes of cell). If these cannot be accurately determined, the model has too many free parameters and is not helpful in defining extrapolated values for risk assessment purposes. This highlights a general problem in using mechanistic models in carcinogen risk assessment, which is that the carcinogenesis data themselves are generally insufficient to define fully the dose response curve shape at low doses or provide much mechanistic information. The analysis is therefore supplemented with policy-based assumptions (such as the expectation of linearity at low doses) and, wherever possible, additional

experimental measurements relating to the mechanism of action, in order to make meaningful prediction of risk from environmental exposures to humans.

Because of the difficulties in validating simplified mechanistic models such as the basic multistage model, and the additional difficulty of parameter estimation with more complex mechanistic models, the new U.S. EPA guidelines (U.S. EPA, 2005a) and some recent California risk assessments have chosen instead to use a less overtly mechanistic approach. This approach combines benchmark dose methodology (described below) with an explicit choice of the method for low-dose extrapolation, either assuming low-dose linearity or, for certain carcinogens where data indicate that this is appropriate, a "margin of exposure" or safety/uncertainty factor based approach. This benchmark method is now normally recommended for carcinogen dose response analysis, and the results generally differ little from those derived by the linearized multistage model. Although the linearized multistage method is no longer recommended as the default approach for cancer potency estimation it remains a plausible alternative in many cases, and still has useful applications, such as for time-to-tumor analyses for which benchmark methods are not yet widely available. Additionally, a considerable number of existing cancer potencies in Appendices A and B, and used in the Air Toxics Hot Spots program were derived by this method. Many of these would not be significantly different if calculated by the benchmark approach, and are unlikely to be replaced soon by newly calculated values. The linearized multistage method will therefore also be briefly described here.

Benchmark dose methodologies

The use of benchmark dose methodology has been explored by various investigators [including Gaylor et al. (1998); van Landingham et al. (2001) and Crump (1984, 1995, 2002)] as a tool for dose response extrapolation. This has been recommended in regulatory guidelines for both carcinogenic (U.S. EPA, 2005a) and non-carcinogenic (U.S. EPA, 1995) endpoints. The basic approach is to fit an arbitrary function to the observed incidence data, and to select a "point of departure" (POD) (benchmark dose) *within the range of the observed data.* From this a low dose risk estimate or assumed safe level may be obtained by extrapolation, using an assumed function (usually linear) or by application of uncertainty factors. The critical issue here is that no assumptions are made about the nature of the underlying process in fitting the data. The assumptions about the shape of the dose response curve (linear, threshold, etc.) are explicitly confined to the second step of the estimation process, and are chosen on the basis of policy, mechanistic evidence or other supporting considerations. The benchmark chosen is a point at the low end of the observable dose-response curve. Usually a dose at which the incidence of the tumor is 10% is chosen for animal studies, although lower effect levels may be appropriate for large epidemiological data sets. Because real experimental data include variability in the response of individual subjects, and measurement errors, likelihood methodology is applied in fitting the data. A lower confidence bound (usually 95%) of the effective dose (LED_{10}), rather than its maximum likelihood estimate (MLE), is used as the point of departure. This properly reflects the uncertainty in the estimate, taking a cautious interpretation of highly variable or error-prone data. It also reflects the instability of MLE values from complex curve-fitting routines, which has been recognized as a problem also with the linearized multistage model.

For cancer dose-response estimation using the benchmark dose method, either animal bioassay data or epidemiological data provide a suitable basis. In the absence of a pharmacokinetic model

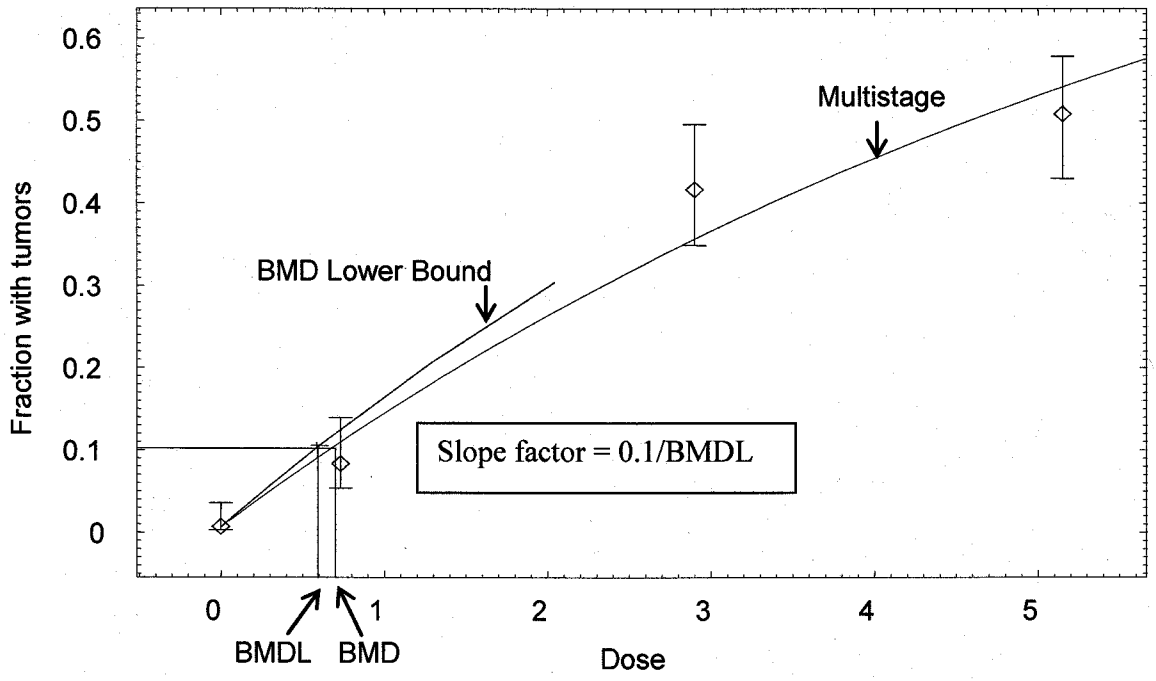
(which could provide tissue-specific dose metrics), the potency would ordinarily be based on the time-weighted average exposure during the exposure or dosing period. The model used to fit the data can be chosen from a range of available alternative quantal models, depending on which provides the best fit to the data in the observable range. In practice, the multistage polynomial fit developed for the linearized multistage model works well for most tumor data sets. Here it is being used merely as a mathematical curve-fitting tool, where the model well fits the data set, without making assumptions about its validity as a biological model of carcinogenesis.

Suitable polynomial fits and estimates of the benchmark may be obtained using U.S. EPA's BMDS software. The benchmark often used is the 95% lower confidence bound on the dose producing 10% tumor incidence. However, if data are available which include a significant dose-response at less than 10% tumor incidence, then that lower benchmark should be used (e.g. LED_{05} or LED_{01}). Other software such as Tox_Risk, which was used for the linearized multistage model, has been used successfully, although the earlier GLOBAL program and its relatives are less suitable as curve-fitting tools for benchmark dose analysis.

Since it is usually assumed in cancer risk estimation that the low-dose response relationship is linear, risk estimates and a potency value (slope factor) may be obtained by linear extrapolation from an appropriate benchmark dose. The potency is the slope of that line ($0.1/LED_{10}$). The low dose linearity assumption is a general default for any carcinogen, and it is unlikely to be altered for genotoxic carcinogens.

A calculation using the benchmark dose approach (using a polynomial model with exponents restricted to zero or positive values), and linear extrapolation from the LED_{10} to obtain a potency estimate is shown in Figure 1 (the figure was generated by the U.S. EPA's BMDS program). This is based on tumor incidence data from an actual experiment with vinyl bromide in rats (Benya *et al.*, 1982), with metabolized dose calculated by means of a pharmacokinetic model (Salmon *et al.*, 1992). The value of q_1^* obtained by this calculation would then be corrected for the duration of the experiment if it had lasted for less than the standard rat lifetime, and for bodyweight and route-specific pharmacokinetic factors as described below. This is in addition to the correction for exposure duration that would be necessary if the study had not lasted for 105 weeks, and the interspecies correction, both of which are described below.

Figure 1. Benchmark dose calculation for tumor data in rats exposed to vinyl bromide



From Salmon *et al.* (1992), based on data from Benya *et al.* (1982)

Linearized Multistage Model

Quantal analyses

A "multistage" polynomial (U.S. EPA, 1986, 2005a; Anderson *et al.*, 1983), based on the mechanistic insights of the original Armitage and Doll model of cancer induction and progression, has been used extensively by U.S. EPA, OEHHA and other risk assessors to model the dose response for lifetime risk of cancer. It usually is used for analysis of animal bioassay data, although related approaches have occasionally been used with epidemiological data. In mathematical terms, the probability of dying with a tumor (P) induced by an average daily dose (d) is:

$$P(d) = 1 - \exp[-(q_0 + q_1 d + q_2 d^2 + ... + q_j d^j)]$$

with constraints

$$q_i \geq 0 \text{ for all i.}$$

Equivalently, $A(d) = 1 - \exp[-(q_1 d + q_2 d^2 + \cdots + q_k d^k)]$,

where $A(d) = \dfrac{P(d) - P(0)}{1 - P(0)}$ is the extra risk over background at dose d.

The q_i model parameters are constants that can be estimated by fitting the polynomial to the data from the bioassay, *i.e.* the number of tumor bearing animals (as a fraction of the total at risk) at each dose level, including the controls. The fit is optimized using likelihood methodology, assuming that the deviations from expected values follow a χ^2 distribution, with the number of degrees of freedom (and hence the maximum number of terms allowed in the polynomial) determined by the number of points in the data set. All the coefficients of the terms are constrained to be zero or positive, so the curve is required to be straight or upward curving, with no maxima, minima or other points of inflection. In addition to the maximum likelihood estimates of the parameters, the upper 95% confidence ~~bounds~~ limits on these parameters are calculated.

The parameter q_0 represents the background lifetime incidence of the tumor. The 95% upper confidence limit of the slope factor q_1~~, or more usually its upper bound~~ (q_1^*), is termed the cancer potency. The maximum likelihood estimate (MLE) of q_1 is not usually regarded as a reliable estimate for several reasons. First, it fails to reflect the uncertainty and variability in the data which affect the value of the estimate. This is an important issue for protection of public health, which is emphasized by current regulatory guidelines. Secondly, due to the variable order of the polynomial and the effect of some terms being zero as opposed to having a small but finite value, the MLE is unstable, and may show large and unpredictable changes in response to very slight changes in the input data. It may also erratically have a zero value, even when the data imply a significant positive dose-response relationship. The MLE is not a measure of central tendency for this estimate distribution (which is always asymmetrical and often multi-peaked). For small doses, the cancer potency is the ratio of excess lifetime cancer risk to the average daily dose received. Details of the estimation procedure are given in Crump (1981) and Crump, Guess, and Deal (1977). Several software programs are available to perform the necessary calculations, including U.S. EPA's BMDS, Tox_Risk and the earlier GLOBAL programs by Crump and colleagues, and Mstage, written by Crouch (1987).

When dose is expressed in units of mg/kg-d, the potency is given in units of $(\text{mg/kg-d})^{-1}$. Likewise, when the model input is in units of concentration ($\mu g/m^3$, ppb), the potency is given in units of $(\mu g/m^3)^{-1}$ pr $(\text{ppb})^{-1}$. As in the case of potencies obtained by the benchmark approach, the experiment-based potency value needs to be corrected for less-than lifetime or intermittent exposure, and extrapolated from the test species to humans. Risk calculations using potency value estimated using the linearized multistage model predict the cancer risk at low doses only, with the higher order terms of the fitted polynomial being ignored since their contribution is negligible at low doses.

Selection of Site and Tumor Type

In developing cancer potency estimates from animal data, standard practice has been to use dose-response data for the most sensitive tumor site as the basis of the estimate (CDHS, 1985). Where tumors of more than one histological type (e.g. adenomas and carcinomas) are observed at a single site, the combined incidence, i.e. proportion of animals affected with at least one tumor of

any of the relevant types, is used for dose-response assessment. The same rules for combining tumor types are generally applied in determining statistical significance for carcinogen identification (IARC, 2006). Tumor types considered to represent different stages of progression following initiation of a common original normal cell type are combined, whereas tumor types having different cellular origins are generally not combined by this procedure. Other considerations that may influence choice of site for dose response estimation include the quality of the data (especially, the statistical impact of a high or variable rate of a particular tumor type and site in control animals), and biological relevance to humans. However, it is an important principle that, just as for the hazard identification phase, concordance of site or tumor type between animal models and human health effects may occur but is not assumed or required.

Carcinogens inducing tumors at multiple sites

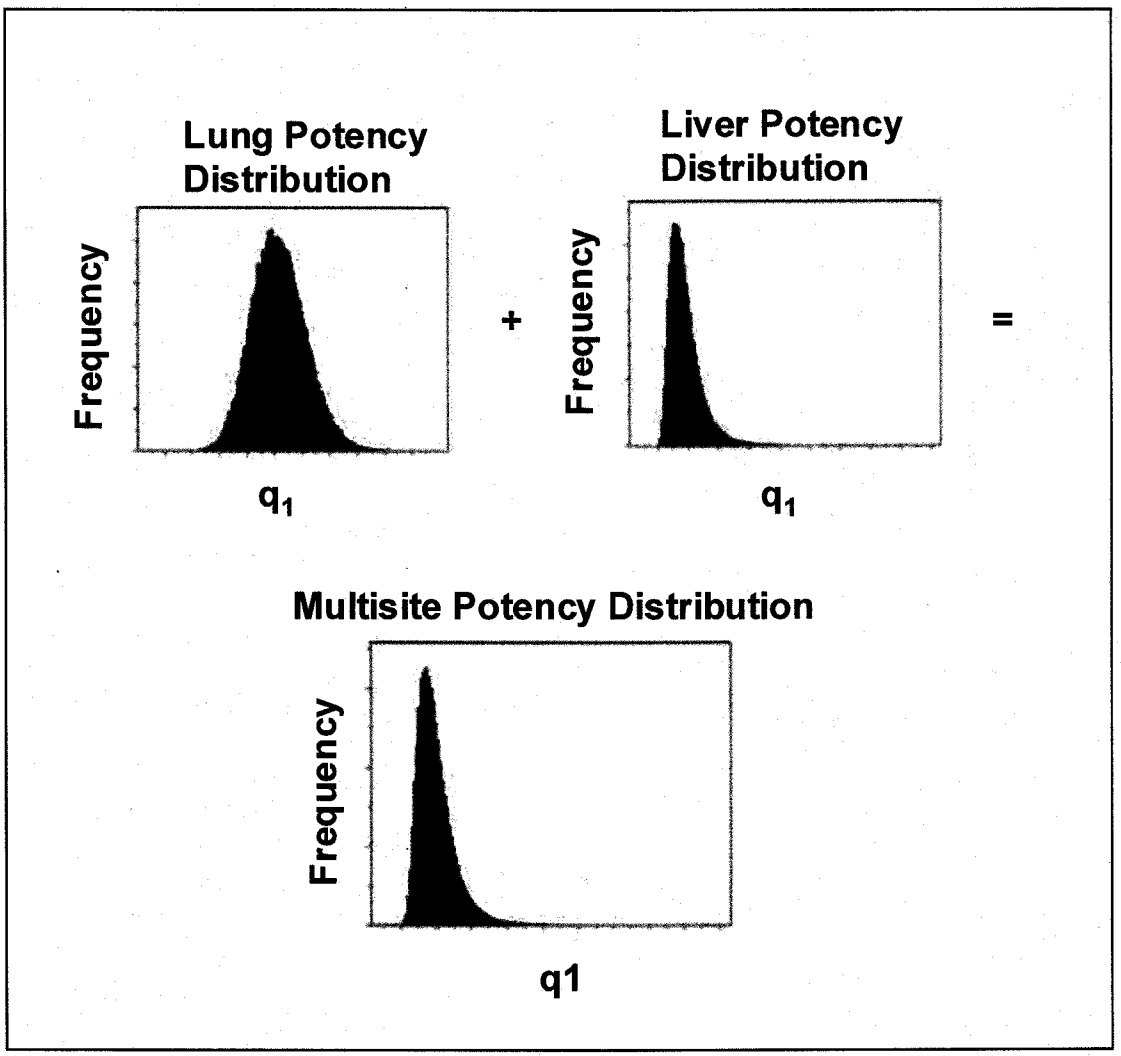
For most carcinogens, the selection of the most sensitive site in the animal studies is recognized as providing a risk estimate which is appropriate to protect human health. However, for chemicals that induce tumors at multiple sites, the single-site approach may underestimate the true carcinogenic potential. For example, the overall assessment of cancer risk from cigarette smoking (U.S. DHHS, 1982) or ionizing radiation (NRC, 1990) is not based on risk at one site, such as lung cancer. Instead, total cancer risk is estimated from all the sites at which agent-induced tumors are observed (lung, bladder, leukemia, etc), combined.

For carcinogens that induce tumors at multiple sites and/or with different cell types in a particular species and sex, OEHHA derives the animal cancer potency by probabilistically summing the potencies from the different sites and/or cell types. Using the combined potency distribution takes into account the multisite tumorigenicity and provides a basis for estimating the cumulative risk of all treatment-related tumors.

The linear term (q_1) of either the multistage model or the multistage-in-dose, Weibull-in-time model is first estimated based on the dose-response data for each of the treatment-related tumor sites. Statistical distributions, rather than point estimates, are generated at each site by tracing the profile likelihood of the linear term (q_1) (Zeise et al., 1991). The distributions of q_1 for each of the treatment-related sites are then statistically summed using a Monte Carlo approach and assuming independence (Figure 2). The sum is created by adding the linear term for each tumor site, according to its distribution, through random sampling. The upper 95 percent confidence limit on the summed distribution is taken as the multisite animal cancer potency estimate (McDonald et al., 2003, McDonald and Komulainen, 2005).

OEHHA has applied this approach in several recent dose-response analyses, including that for naphthalene presented in Appendix B of this document.

Figure 2. Addition of potency distributions for multi-site cancer potency derivations.



Early-Lifestage Cancer Potency Adjustments

In recent years, there have been growing concerns regarding the exposure of children to environmental chemicals, including the possibility that they may be more susceptible than adults to injury caused by those chemicals. The California Legislature passed the Children's Environmental Health Protection Act (Senate Bill 25, Escutia; Chapter 731, Statutes of 1999; "SB 25") to help address these concerns. Under SB25, OEHHA is mandated to consider infants and children specifically, where data permit, in evaluating the health effects of Toxic Air Contaminants (TACs).

The development of cancer is one of the adverse health effects that may occur in children as a result of exposure to environmental chemicals. The document "Prioritization of Toxic Air Contaminants under the Children's Environmental Health Protection Act" (OEHHA, 2001a) noted that risks of cancer from exposures to carcinogens occurring from conception through puberty can be different than those from exposures occurring in adulthood. Exposure to a carcinogen early in life may result in a greater lifetime risk of cancer for several reasons:

1. Cancer is a multistage process and the occurrence of the first stages in childhood increases the chance that the entire process will be completed, and a cancer produced, within an individual's lifetime.
2. Tissues undergoing rapid growth and development may be especially vulnerable to carcinogenic agents. During periods of increased cell proliferation there is rapid turnover of DNA, and more opportunity for misrepair of damage (e.g., DNA breaks, crosslinks, adducts) or alterations to result in permanent changes to the DNA (e.g., mutations, altered DNA methylation) that may ultimately lead to cancer.
3. During early development, a greater proportion of the body's cells are relatively undifferentiated stem cells, and as such represent a large target population of somatic cells capable of passing along permanent changes to the DNA during future cell divisions.
4. There may be greater sensitivity to hormonal carcinogens early in life since the development of many organ systems is under hormonal control (e.g., male and female reproductive systems, thyroid control of CNS development).
5. Other factors that may play a role in increased cancer risk from exposures during critical developmental periods include differences in immunological activity, intestinal absorption, biliary and kidney excretion, blood and fat distribution, and expression of enzyme systems that activate or detoxify carcinogens.

Data in humans and animals for a variety of carcinogens suggest that exposures to such carcinogens early in life may result in a greater lifetime risk of cancer compared to exposures later in life. Examples of this effect in humans are carcinogenicity due to ionizing radiation, diethylstilbestrol (DES), chemotherapeutic agents, and tobacco smoke.
Ionizing radiation exposure carries an increased risk of cancer when exposures occur early in life compared to adult exposures for a number of tumor types. Children exposed to ionizing radiation (diagnostic X-rays) *in utero* demonstrate a larger excess of leukemia cases than

children exposed to ionizing radiation postnatally (NRC, 1990). Exposure to radioisotopes (^{131}I, ^{137}Cs, ^{134}Cs, ^{90}Sr) as a consequence of the 1986 Chernobyl nuclear accident resulted in an elevated thyroid cancer incidence in children but not adults (Moysich, 2002). Treatment of children for Hodgkins lymphoma with both chemotherapeutic agents and irradiation has been shown to increase the risk of secondary tumors (Swerdlow et al., 2000; Franklin et al., 2006). Age at irradiation in Hodgkin's disease patients treated with radiotherapy strongly influenced the risk of developing breast cancer. The relative risk (RR) of developing breast cancer was 136 for women treated before 15 years of age, 19 for women 15-24 years of age, and 7 for those 24-29 years of age. In women above 30 years of age, the risk was not increased (Hancock *et al.*, 1993).

DES was administered to pregnant women in the 1940s-1960s for the purpose of preventing pregnancy loss. In 1970, Herbst and Scully described 7 cases of vaginal adenocarcinoma (6 cases of the clear-cell type) in women aged 15-22 years. This type of cancer is extremely rare in that age range. A follow-up epidemiological study included an additional case, and noted the fact that the mothers of 7 of the 8 patients had been treated with DES during their pregnancy (Herbst *et al.*, 1971). Reports by other investigators confirmed the association between maternal use of DES during pregnancy and the development of vaginal adenocarcinoma in their female offspring (Preston-Martin, 1989). It was observed that *in utero* DES exposure resulted in female genital tract morphological changes which correlated with both dose and duration of exposure, and those changes were not related to the maternal conditions which were the reason for the DES administration. Additionally, the risk of occurrence of those morphological changes declined with increasing gestational age at first exposure (O'Brien *et al.*, 1979; Preston-Martin, 1989). In contrast, vaginal adenocarcinoma incidence did not increase in the exposed mothers themselves, indicating an increased early-life susceptibility to the carcinogenic effects of DES.

There is evidence in the epidemiological literature indicating that exposure to tobacco smoke during puberty may increase risk of breast cancer later in life, particularly among women who are NAT2 slow deacetylators (Marcus *et al.*, 2000; Morabia *et al.*, 2000; Lash and Aschengrau, 1999). Wiencke et al. (1999) report that early age at initiation of smoking is associated with a higher level of DNA adducts in lung tissue of former-smokers with lung cancer.

It has also been observed by Smith *et al.* (2006) that human *in utero* or early childhood exposure to arsenic in drinking water results in significantly increased lung cancer incidences during adult life.

Data from animal studies provide additional examples of increased sensitivity to early life (typically postnatal and juvenile) exposures. These effects span a range of target tissues, including the liver (vinyl chloride, safrole), brain (methylnitrosourea), reproductive tract (DES, tamoxifen), and lung (urethane) (OEHHA, 2001a).

In the following sections we summarize two efforts to evaluate quantitatively the effect of lifestage at exposure on carcinogenic response in experimental animal studies. The first section provides a description of OEHHA's analysis of data on the effect of age at exposure on carcinogenic potency. (Details of this analysis are in Appendix J.) The second section describes U.S. EPA's work in this area. (We also provide the published paper in Appendix I that presents the U.S. EPA analyses.) Both analyses used extant data available in the published literature. U.S. EPA used their analysis to modify the procedures they have used to estimate cancer risk by

weighting risk by specific factors for childhood exposures. The weighting factors are a policy choice supported by U.S. EPA's data analysis. The results of OEHHA's analysis, summarized below and described in detail in Appendix J, support the decision to modify policy to weight risk when exposure occurs during childhood. Thus, OEHHA is also proposing to weight risk when exposure occurs in childhood.

OEHHA Analysis of the Effect of Age at Exposure on Cancer Potency

The analysis of animal cancer studies which include early life exposure by the Reproductive and Cancer Hazard Assessment Branch (RCHAB) of OEHHA also supports the application of lifestage-specific cancer potency factor adjustments. This analysis is provided in detail as Appendix J of this document.

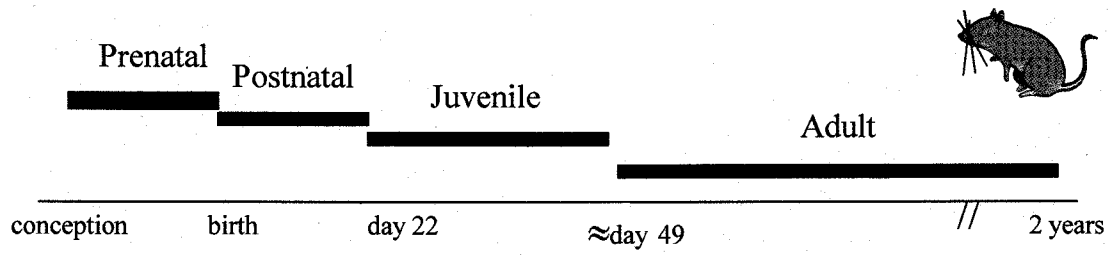
Early-in-life susceptibility to carcinogens has long been recognized by the scientific community and clinicians as a public health concern. Numerous scientific publications and symposia have addressed this issue over the years and the scientific literature contains a number of human clinical findings and epidemiological studies of early life cancer susceptibility. While there are many indications of increased human cancer susceptibility in early life, the magnitude of the impact has been difficult to gauge. Until recently risk assessment procedures have not in general addressed the issue. As described in the next section, in 2005 the U.S. EPA adopted an approach to weight carcinogens by age at exposure if they act via a mutagenic mode of action. The California legislature in 2000 directed OEHHA to assess methodologies used in addressing early-in-life risk, compile animal data to evaluate those methods, and develop methods to adequately address carcinogenic exposures to the fetus, infants, and children (Children's Environmental Health Initiative [AB 2872, Shelly]; California Health and Safety Code [HSC] section 901 [a] through [e]).

OEHHA assessed cancer risk assessment methodologies, and found that the existing risk assessment approaches did not adequately address the possibility that risk from early-in-life and adult exposures may differ. OEHHA further concluded that there was a need to address early-in-life cancer risk, and undertook studies to develop methods for doing so. Age-related cancer susceptibility data were identified from published animal cancer bioassays in which these issues were addressed. Two types of studies with early-in-life exposures were compiled. The first type are "multi-lifestage exposure studies." These studies have at least two groups exposed during different lifestages: One dose group is exposed to a chemical only during one of the following lifestages (Figure 3):

- prenatal (from conception to birth),
- postnatal (from birth to weaning),
- juvenile (from weaning to sexual maturity).

The second dose group is exposed for some period of time at an older age, preferably during the adult lifestage, that is, after sexual maturity. This group served as the reference group. In some cases where there was no adult exposure group, animals exposed as juveniles served as the reference group. Multi-lifestage exposure studies are available for many chemicals, enabling the exploration of patterns in early-life susceptibility across chemicals.

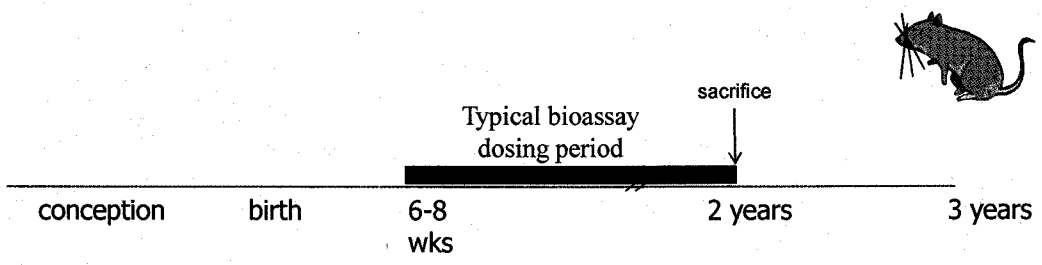
Figure 3. Definition of Rodent Lifestage Adopted in the OEHHA Analyses



OEHHA also conducted "chemical-specific case studies" of early-life sensitivity for two carcinogens, ethyl-N-nitrosoamine (DEN) and N-ethyl-N-nitrosourea (ENU) that combine data from a number of studies. These "chemical-specific case studies" were conducted to explore the feasibility of analyzing chemical-specific data on age susceptibility from single-lifestage exposure experiments. For these chemicals, OEHHA compiled from the literature a second type of study, "single-lifestage exposure experiments." In these experiments dose groups were exposed only during a particular lifestage and, unlike the "multi-lifestage exposure studies," there was no requirement that the same study also include groups exposed during a different lifestage. Thus, single-lifestage exposure experiments were identified as being either prenatal, postnatal, juvenile, or adult exposure studies. For each of the two chemicals, there were many prenatal studies conducted that were compiled, analyzed, and grouped together. Postnatal studies from different publications were similarly compiled, analyzed and grouped together, as were juvenile studies. Adult studies were not available for either DEN or ENU, thus for both chemicals juvenile exposure studies served as the referent for prenatal studies, and for postnatal studies.

Typical cancer bioassays such as those conducted in rats and mice by NTP involve exposing animals starting at six to eight weeks of age, which is the time at which these animals reach sexual maturity (late teenagers relative to humans). The experiments are run for two years, ending when the animal is in late middle age. Thus, early and very late life exposures are not included in the typical rodent bioassay (see Figure 4). If the NTP bioassay is used as a basis for estimating cancer potency, the potency and resulting risk estimates may be too low. Thus OEHHA focused on finding studies that evaluated early in life exposures.

Figure 4. Dosing Period for Typical Rodent Bioassays.



Since bioassays examining the effect of age at exposure on carcinogenesis were conducted by various investigators for different purposes, there is a great deal of variation across studies in terms of dose selection, duration of exposure, number of animals, and length of study duration. To be included in the compilation of studies with early life exposure, a study or an experimental group in a study had to meet minimum requirements.

The criteria for study inclusion are as follows:

- Treated groups were exposed to a single chemical carcinogen or a single carcinogenic chemical mixture.
- Study groups were not compromised by severe treatment-related non-cancer toxicity.
- Overall the duration of exposure period plus observation period exceeded 40 weeks, unless animals died of tumor.
- For included dose groups, the study must report age at dosing, age at sacrifice, and site-specific tumor incidence.
- Each lifestage exposure treatment group has an appropriate concurrent control group, or, for rare tumors only, an appropriate historical control.
- The studies were on mammals.
- Each treatment and control group consists of at least ten animals, unless the conduct and design of the study was well done in all other aspects (e.g., the length of the study was sufficiently long to observe treatment-related tumors) and tumor incidence was high in treated groups and very low in controls.
- Site specific tumor data were reported, not only total number of tumor bearing animals.
- The test compound was administered in the diet, water, via gavage, or by intraperitoneal (i.p.), intravenous (i.v.), or subcutaneous (s.c.) injection. For dermal and subcutaneous injection studies, distal tumor findings are utilized (for dermal, other than skin tumors; for injection, non-injection site tumors).

- While studies designed to histopathologically examine tumors at multiple sites were preferred, studies that examined only a select set of organ/tissue sites were not excluded if the sites examined were known with confidence to be the only target tissues for the chemical and lifestage in question in that particular strain of animal.

Different approaches were taken to identify animal cancer studies that included groups of animals exposed during early life stages. First, MEDLINE and TOXLINE (National Library of Medicine) databases were searched using combinations of various key words for cancer (e.g., tumor(s), neoplasm(s), cancer, neoplasia, cancerous, neoplasms-chemically induced) and for early-life exposure (e.g., age, age-at-exposure, development (al), prenatal, *in utero*, gestation (al), postnatal, neonatal, juvenile, weaning, weanling, adolescent, adolescence, young). Second, the extensive compilation of bioassays in the *Survey of Compounds which have been Tested for Carcinogenic Activity*, was reviewed. This survey, formerly maintained by the National Cancer Institute as Public Health Service Publication Number 149, or PHS 149, is now available from a private source electronically as CancerChem, 2000. Third, from bibliographies from relevant published papers additional studies were identified. Finally the Single Dose Database developed by Calabrese and Blain (1999) was obtained and utilized to identify additional publications that appeared to contain potentially useful data. All of these publications were evaluated to determine if the study dosed separate groups of animals early in life and at or near adulthood. A total of 145 publications, providing data on 84 chemicals, were identified as meeting the criteria for study inclusion. A subset of these met the criteria for inclusion in the multi-lifestage exposure analysis.

Finally, for the OEHHA multi-lifestage analyses, we define "experiment" as a study component consisting of a control group as well as a treated group(s) exposed during the same lifestage (i.e., prenatal, postnatal, juvenile or adult), and using the same experimental protocol (e.g., route of exposure, strain, species, laboratory). Thus, by our definition one publication may report multiple experiments.

In the OEHHA analysis, data from studies on 23 unique carcinogens, 20 of which are considered to act via primarily genotoxic modes of action, were analyzed. Of these 20 carcinogens, 15 are thought to require metabolic activation to the ultimate carcinogenic species (Table 1~~Table 1Table 1~~). Fourteen carcinogens, including one thought to act via primarily nongenotoxic modes of action, were included in the prenatal multi-lifestage exposure studies. Eighteen carcinogens, including two thought to act via primarily nongenotoxic modes of action, were included in the postnatal multi-lifestage exposure studies. Five carcinogens were included in the juvenile multi-lifestage exposure studies. The case study chemicals, DEN and ENU, are both genotoxic. ENU is a direct acting alkylating agent, while DEN requires metabolic activation.

Table 1. Carcinogens for which studies with multi-lifestage exposures in animal studies are available

Genotoxic carcinogens requiring metabolic activation
Benzidine Benzo[a]pyrene Dibutylnitrosamine Diethylnitrosamine (DEN) 7,12-Dimethylbenz[a]anthracene (DMBA) Dimethylnitrosamine (DMN) Di-n-propylnitrosamine (DPN) 1 -Ethyl-nitrosobiuret 2-Hydroxypropylnitrosamine 3-Hydroxyxanthine 3-Methylcholanthrene (3-MC) 4-(Methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK) Safrole Urethane Vinyl chloride
Genotoxic carcinogens not requiring metabolic activation
Butylnitrosourea 1,2-Dimethylhydrazine Ethylnitrosourea (ENU) Methylnitrosourea (MNU) ß-Propiolactone
Nongenotoxic carcinogens
1,1-Bis(p-chlorophenol)-2,2,2-trichloroethane (DDT) Diethylstilbestrol (DES) 2,3,7,8-Tetrachlorodibenzodioxin (TCDD)

Cancer Potency Estimation

Statistical methods were developed and used to analyze the data and derive measures of early-life susceptibility. These are described in detail in Appendix J. In brief, a cancer potency (the slope of the dose response curve) was developed for each of the experiments selected using the linearized multistage model. This model was chosen because of widespread use in risk assessment, and its flexibility in being able to fit many different data sets needed to evaluate the effect of lifestage-at-exposure on cancer potency. The dose metric used for the potency analyses is cumulative dose normalized to body weight. The cancer potency is thus expressed as the increase in tumor probability with increasing cumulative dose in units of mg/kg body weight.

To take into account uncertainty in potency estimation, cancer potencies are depicted by a statistical distribution, rather than by a single, fixed value, using methods described in Appendix J. While these methods have typically been used to obtain and report the 95th percentile of the cancer slope parameter for cancer risk assessment purposes, here OEHHA utilized the full distribution of the cancer slope parameter to derive measures of early-life susceptibility to carcinogens. This was done to systematically take into account uncertainty in the analysis.

For experiments where treatment related tumors were observed at multiple sites or at the same site but arising from different cell types, slopes from these sites were statistically combined by summing across the potency distributions (assuming independence across the sites that were observed) to create an overall multisite cancer potency. It is not uncommon that a carcinogen causes more than one type of cancer or causes tumors at different sites depending on lifestage at exposure. For example, in humans tobacco smoke causes cancers of the lung, bladder, and certain other organs. This multi-site carcinogenicity is frequently observed in animal experiments as well. In order to account for this, all treatment-related tumors that were observed in a given lifestage were taken into account in estimating cancer potency from that particular experiment.

Addressing Early-Age Sensitivity in Estimating Cancer Risk: Age Sensitivity Factors

Inherent Sensitivity of Lifestages – Lifestage Potency Ratios

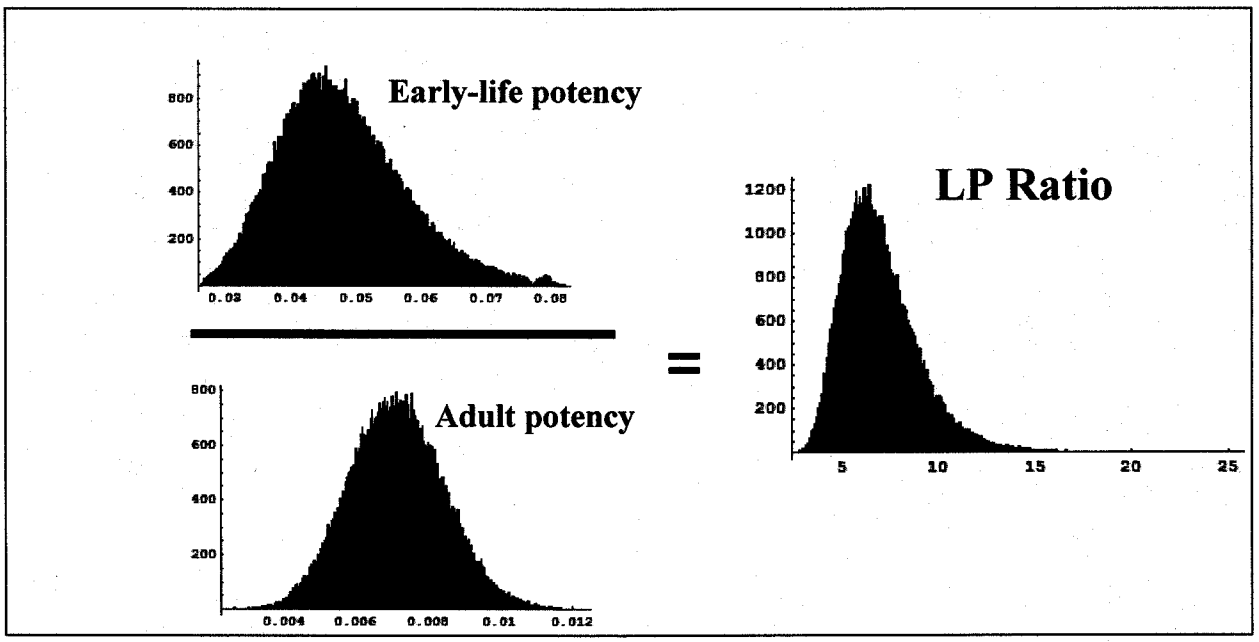
For this analysis, OEHHA calculates the ratio of cancer potency derived from an early lifestage exposure experiment(s) to that derived from an experiment(s) conducted in adult animals. OEHHA used the potency distributions for the individual lifestage exposures, rather than a point estimate, to derive the ratios. The lifestage cancer potency ratio is then described as a distribution and one can select specific percentiles from the distribution to better understand and bound the uncertainty (Figure 5). Of particular importance is the location of the ratio distribution in relation to the reference value of 1.0, which would mean no difference in risk from exposures at early versus adult lifestages. A lifestage cancer potency ratio distribution that primarily lies above the value of 1.0 indicates early life exposures to a carcinogen result in a stronger tumor response relative to adult exposure. Conversely, a lifestage cancer potency ratio distribution that mainly lies below the value of 1.0 indicates early life exposure to a carcinogen results in a weaker tumor response relative to adult exposure.

A lifestage potency (LP) ratio distribution was derived for each multi-lifestage study, resulting in 22 prenatal ratio distributions representing 14 unique carcinogens, 55 postnatal LP ratio distributions representing 18 unique carcinogens, and seven juvenile LP ratio distributions representing five unique carcinogens. The LP ratio distributions for a given early lifestage were combined into a single "LP ratio mixture distribution," in order to show the range of susceptibilities of that lifestage to the carcinogens studied.

LP ratio mixture distributions for a given early lifestage were developed by (1) obtaining a single LP ratio distribution for each chemical (when a chemical is represented by more than one study) and then (2) equally sampling across all chemicals. When a chemical is represented by more than one study, then the LP ratio distributions from all studies of that chemical were combined by equally sampling from each LP ratio distribution via Monte Carlo methods to obtain a single

LP ratio distribution for that chemical. (Appendix J describes this in more detail, as well as a sensitivity analysis that included two alternative sampling methods.) Once each chemical is represented by a single LP ratio distribution, then the LP ratio mixture distribution for each early lifestage (prenatal, postnatal, and juvenile) is obtained by equally sampling across all of the chemicals via Monte Carlo methods.

Figure 5. Lifestage Potency Ratio (LPR) distribution.

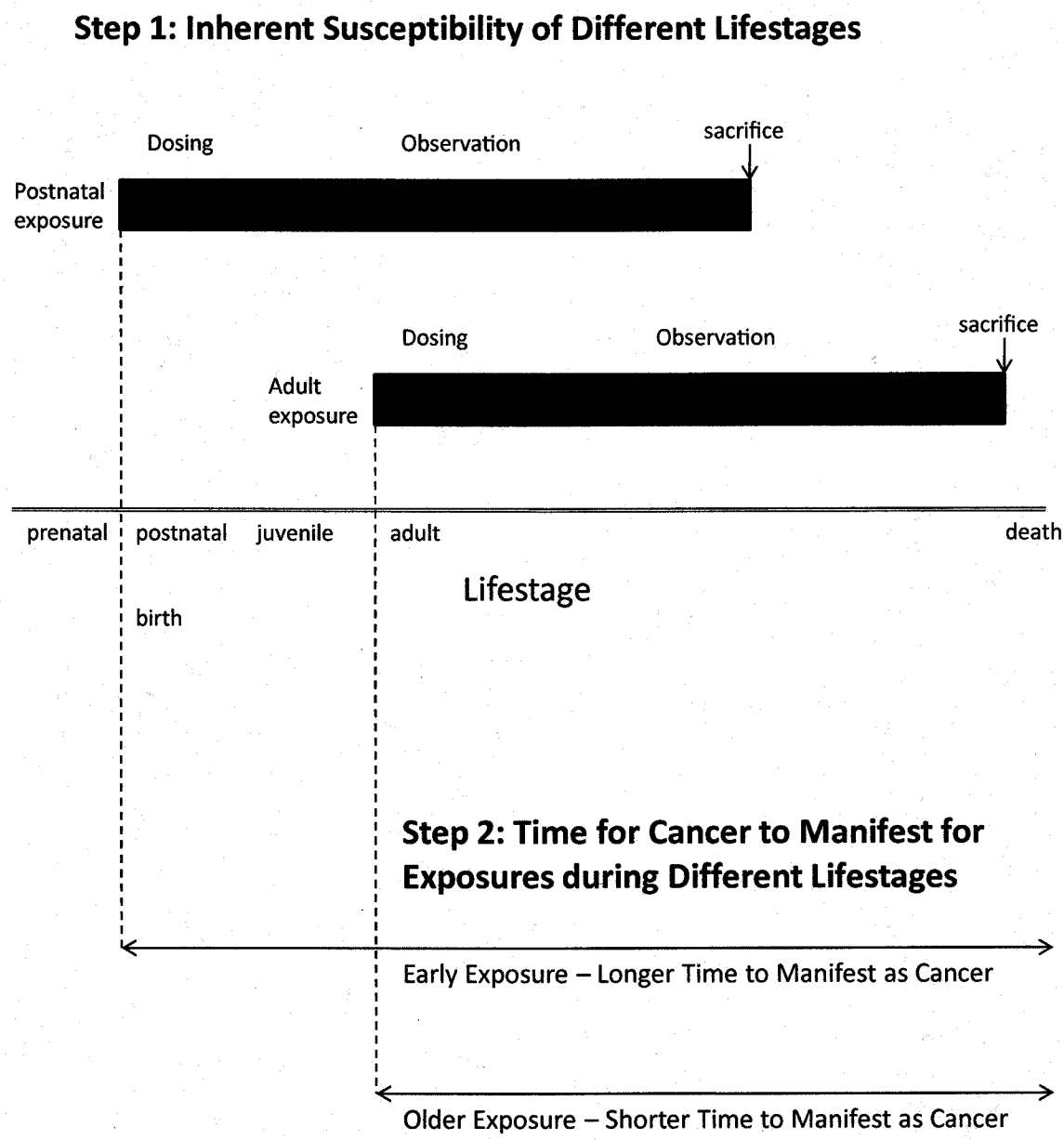


Effect of longer time period for cancer to manifest

The LP ratios described above characterize the inherent susceptibility of early lifestages to carcinogen exposure, by comparing potencies for individuals followed for similar periods of time and similarly exposed, but exposed during different lifestages. Age-specific adjustments to the cancer potency must also take into account the longer period of time that carcinogen exposure to the young has to manifest as cancer. Empirical data from studies of both humans and animals demonstrate that, for many cancers, cancer risk increases with age, or time since first exposure. While some cancers have been seen to increase by as much as the sixth power of age, a general approach taken for example by the National Toxicology Program in analyzing tumor incidences in its chronic bioassays is to assume that cancer risk increases by the third power of age. Thus, consistent with the approach used by the NTP in analyzing rodent cancer bioassay data, the longer period of time that exposed young have to develop tumors is addressed by taking into account time-of-dosing. This was done by multiplying the LP ratio by a time-of-dosing factor, to yield an age sensitivity factor (ASF). Specifically, the prenatal LP ratio is multiplied by a factor of 3.0, the postnatal LP ratio is multiplied by a factor of 2.9, and the juvenile LP ratio is multiplied by 2.7. Thus, ASFs were developed for each experiment, by first calculating the LP ratio to address inherent susceptibility of early lifestages relative to adults, and then accounting for the effect of years available to manifest a tumor following carcinogen exposure. (see Figure

6). Note that we are not using the term "sensitivity" in the immunologic sense (e.g., sensitization), but rather are using the term more generically.

Figure 6. Issues addressed by the Age-Sensitivity Factor (ASF)



Application of this approach for risk associated with lifetime exposures would include an ASF of less than 1 for exposures during the latter part of adult life for carcinogens that act on early stages. Therefore, the addition of this adjustment to the younger lifestages but not to the later part of the adult period could overestimate the risk of whole-life exposures. On the other hand, the 70 year "lifetime" used in estimating lifetime cancer risk does not reflect the longer lifespan of the U.S. population. Further, as noted above, the animal bioassays on which potency was based typically exclude pre-weaning dosing and sacrifice animals during their late middle-age. Use of cancer potencies calculated from standard assays can therefore understate lifetime cancer risk. The ASF calculated for carcinogens includes both inherent sensitivity of developing animals and the available time since exposure to develop cancer.

Results of OEHHA Analysis

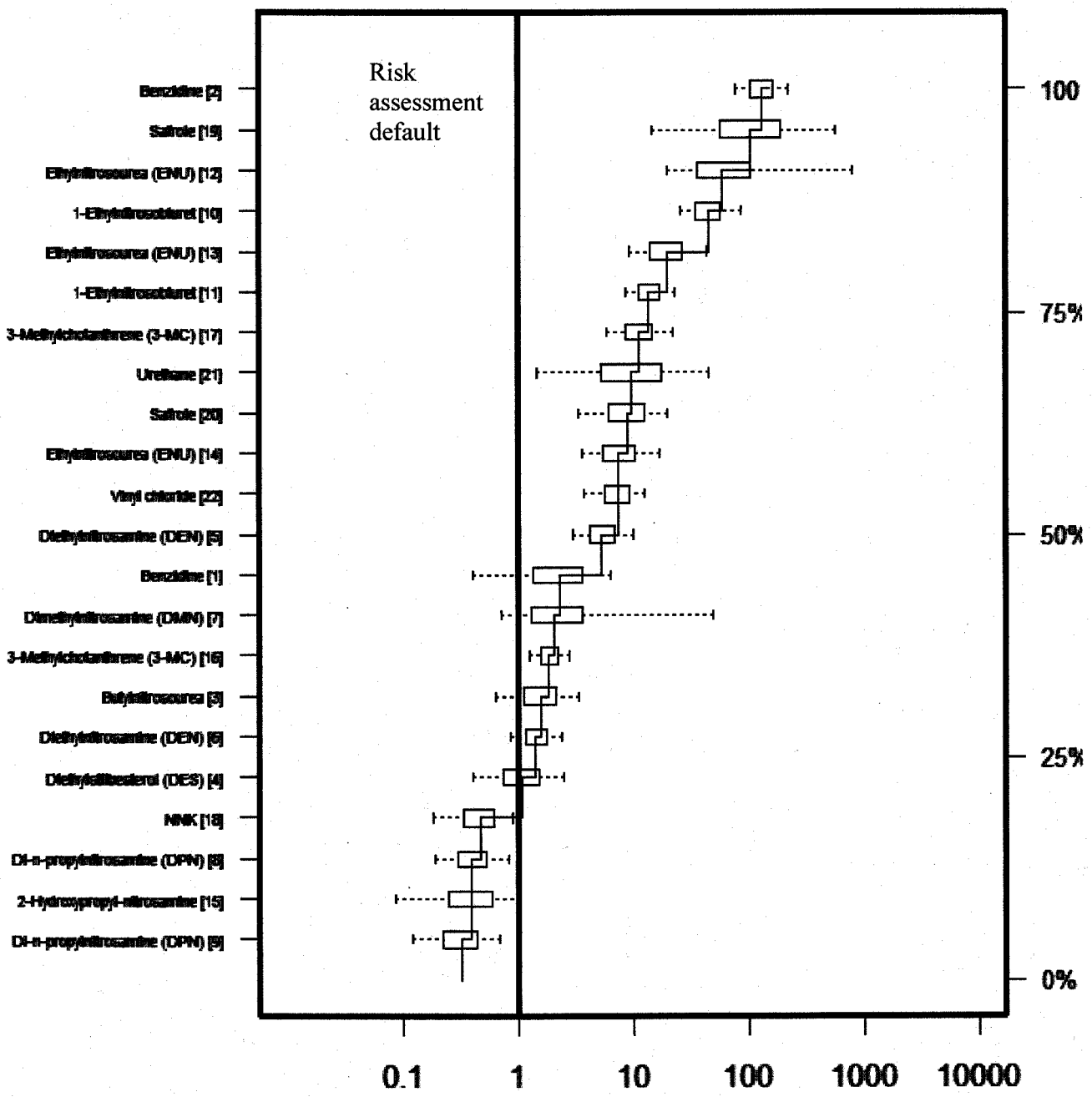
The analyses indicate that both the prenatal and postnatal lifestages can be, but are not always, much more susceptible to developing cancer than the adult lifestage. The analyses also indicated that the ASFs for these age windows vary by chemical, gender and species.

Regarding prenatal lifestage exposure, few cases were indicative of equal inherent adult and prenatal susceptibility, with an LP ratio of unity. The LP ratio distribution was roughly bimodal, with LP ratios for several studies significantly greater than unity and several others significantly less than unity. Figure 7 below shows the ASFs from each of the prenatal multi-lifestage exposure studies, displayed as a cumulative frequency profile. The median of the prenatal ASF mixture distribution was 2.9 (see also Table 6 in Appendix J),

The modality in the prenatal LP ratio distribution was reflected in the DEN and ENU case studies, with results for DEN suggesting inherently less sensitivity than older animals from exposure *in utero*, and for ENU just the opposite. For the DEN and ENU case studies, the referent groups were juvenile rather than adult animals, and the results may have underestimated the LP ratio and ASF, to the extent that some of the apparent sensitivity for DEN and ENU in the prenatal period carries through to the juvenile period. ENU is a direct acting carcinogen that does not require metabolic activation, whereas DEN can not be metabolized to any significant extent by fetal tissues until relatively late in gestation. This may explain the lower fetal susceptibility of DEN. However, prenatal metabolic status is not the sole determinant of prenatal susceptibility; e.g., benzidine and safrole require metabolic activation and exhibit greater susceptibility from prenatal exposure.

The median of the postnatal ASF mixture distribution was 13.5 (see Table 7 in Appendix J). Figure 8 below shows the ASFs from each of the postnatal multi-lifestage exposure studies, displayed as a cumulative frequency profile. Thus, for the chemicals studied, there was generally greater susceptibility to carcinogens during the early postnatal compared to the adult period, particularly when the ASF accounts for the longer period cancer has to manifest when exposure occurs early in life. The DEN and ENU case studies also exhibited substantial extra susceptibility during the postnatal period. To summarize, for most of the carcinogens studied here, animals are inherently more sensitive in the postnatal period, as indicated by Figure 8.

Figure 7. Prenatal ASF Cumulative Frequency Profile



The median of the prenatal ASF mixture distribution was 2.9 (see also Table 6 in Appendix J).
References are given in the legend on the next page