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ENVIRONMENTAL ASSESSMENT OF THE PROPOSED EFFLUENT GUIDELINES FOR THE PHARMACEUTICAL MANUFACTURING INDUSTRY

Volume I

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EXECUTIVE SUMMARY

The Environmental Assessment of the Pharmaceutical Manufacturing Industry quantifies water quality-related benefits for AC and BD facilities[1] based on site specific analyses of current conditions and the conditions that would be achieved by steam stripping process changes. Instream pollutant concentrations from direct and indirect discharges are estimated using stream dilution modeling. The benefits to aquatic life are projected by comparing the modeled instream pollutant concentrations to EPA aquatic life criteria guidance or to toxic effect values. Human health benefits are projected by: (1) comparing estimated instream concentrations to health-based water quality toxic effect values or criteria; and (2) estimating the potential reduction of carcinogenic risk and non-carcinogenic hazard from consuming contaminated fish or drinking water. Upper-bound individual cancer risks, population risks, and non-cancer hazards are estimated using modeled instream pollutant concentrations and standard EPA assumptions. Modeled pollutant concentrations in fish are used to estimate cancer risk and non-cancer hazards among the general population, sports fishermen and their families, and subsistence fishermen and their families. Inhibition of POTW operations and sewage sludge contamination are also evaluated based on current and steam stripping pretreatment levels. Inhibition of POTW operations are estimated by comparing modeled POTW influent concentrations to available inhibition levels.

The modeling for this analysis was orginally performed using the EPA distillation process change as the proposed treatment option. The results of this initial analysis showed limited environmental gains beyond current treatment. Subsequently, steam stripping was selected by EPA as the proposed treatment option. The overall projected loads from these two treatment technologies are roughly comparable. Therefore, although distillation is a more effective treatment technology for removing volatile organic pollutants than is steam stripping, the initial analysis was rerun using the steam stripping pollutant loads only for those facilities for which

[1]AC facilities use fermentation or chemical synthesis processes and BD facilities use extraction, mixing, compounding and formulating processes.

aquatic life or human health criteria excursions, or POTW inhibition problems were projected at current loadings.

The water quality modeling results for 14 direct AC facilities discharging to 14 receiving streams indicate that at **current** discharge levels, instream concentrations of 2 pollutants are projected to exceed **chronic aquatic life criteria** or toxic effect levels in 7 percent of the receiving streams. Instream concentrations of 3 pollutants (using a target risk of 10^{-6} for carcinogens) are projected to exceed **human health criteria** (developed for consumption of water and organisms) in 14 percent of the receiving streams. **Steam stripping** is projected to eliminate all **aquatic life** and **human health** excursions. No excursions of **aquatic life criteria** or toxic effect levels or of **human health criteria** or toxic effect levels are projected at **current** or **steam stripping** discharge levels for 3 direct BD facilities discharging to 3 receiving streams.

Modeling results for 61 indirect AC facilities which discharge to 43 POTWs on 42 receiving streams indicate that at **current** or **steam stripping** discharge levels, instream pollutant concentrations are not projected to exceed **chronic aquatic life criteria** or toxic effect levels. At **current** discharge levels, instream concentrations of 4 pollutants (using a target risk of 10^{-6} for carcinogens) are projected to exceed **human health criteria** or toxic effect levels (developed for consumption of water and organisms) in 10 percent of the receiving streams. Projected excursions of **human health criteria** are reduced to 1 pollutant in 5 percent of the receiving streams at **steam stripping pretreatment** discharge levels. Results for 55 indirect BD facilities which discharge to 45 POTWs on 45 receiving streams indicate instream concentrations of 1 pollutant are projected to exceed **chronic aquatic life criteria** or toxic effect levels in 2 percent of the receiving streams at **current** discharge levels. Instream concentrations of 1 pollutant (using a target risk of 10^{-6} for the carcinogens) are projected to exceed **human health criteria** or toxic effect levels (developed for consumption of water and organisms) in 2 percent of the receiving streams. No excursions of **aquatic life** or **human health criteria** are projected at **steam stripping** discharge levels.

In addition, the excess annual cancer cases at **current** and, therefore, at **steam stripping** treatment levels are projected to be far less than 1 from the ingestion of contaminated fish and drinking water for AC and BD direct and indirect discharges. No systemic toxic effects are projected at the **current** treatment level or at the **steam stripping** treatment level. Seven pollutants are projected to contribute to POTW inhibition at 13 percent of the 46 POTWs receiving the discharge from AC facilities. These POTW impacts are projected to be reduced to three pollutants causing POTW problems at 11 percent of the POTWs by **steam stripping**. No inhibition problems are projected at the 50 POTWs receiving discharges from BD facilities at **current** or **steam stripping pretreatment** levels. No sewage sludge regulatory standards are available for the pollutants analyzed to evaluate potential sludge contamination problems.

The Environmental Assessment of the Pharmaceutical Manufacturing Industry also evaluates air quality-related benefits. Air quality-related benefits are quantified based on potential risks to the general public from on-site fugitive emissions from open-air biological treatment using air dispersion modeling. Two modeling estimates are made based on reductions in pollutant loads - one based on 308 questionnaire loading data ("**low** estimate") and one based on conservative engineering loading estimates ("**maximum** estimate"). Potential risks to POTW maintenance workers from occupational exposure to a mixture of gases partitioning from influent wastewater were also quantified by comparing modeled vapor-phase pollutant concentrations to ACGIH Threshold Limit Values (TLVs).

The air dispersion modeling results of EPA's release estimates indicate that, based on the "**low** estimate", the estimated number of people exposed to risk levels greater than 10^{-6} would be reduced by approximately 190,000. This would result in a reduction of 0.023 annual cancer cases. Based on estimates of the "**maximum** benefit" of regulating emissions, there would be a benefit of 0.35 annual cancer cases. Exposure to pollutants released from pharmaceutical manufacturing facilities are projected to exceed TLVs for POTW workers at 12 POTWs treating 52 pollutants at **current** discharge levels. At **distillation pretreatment** discharge levels, TLVs are projected to be exceeded at 7 POTWs treating 44 pollutants. At **steam stripping**

pretreatment discharge levels, which are slightly higher than distillation pretreatment discharge levels, TLVs are projected to be exceeded at 6 to 12 POTWs treating 52 pollutants.

Documented environmental impacts on aquatic life, human health, and POTW operations from pollutant discharges from pharmaceutical manufacturing facilities are summarized in the Environmental Assessment of the Pharmaceutical Manufacturing Industry. The summary data are based on a review published scientific literature, newspaper articles, and survey data. A total of 16 studies reported environmental impacts from pharmaceutical manufacturing. These impacts included: (1) human health effects (general population and occupational exposure) such as dizziness, nausea, respiratory and dermal problems and endocrine dysfunction (reproductive); (2) aquatic life effects, such as fish kills; (3) effects on the quality of receiving water, groundwater, soils, sediments, and drinking water; and (4) impairment of POTW operations. Four pharmaceutical manufacturing facilities are identified by States as being point sources causing water quality problems and are included on their CWA Section 304(l) short list for discharges of toxics.

1. INTRODUCTION

The purpose of this report is to present (1) an assessment of the water quality benefits of controlling the discharge from pharmaceutical manufacturing facilities to surface waters and publicly-owned treatment works (POTWs), and (2) an assessment of the air quality benefits of controlling on-site fugitive emissions to ambient air from open-air wastewater treatment at pharmaceutical manufacturing facilities and volatization of chemical discharges at POTWs. Potential aquatic life and human health impacts of direct discharges on receiving stream water quality and of indirect discharges on POTWs and their receiving streams are projected at current and steam stripping treatment levels by quantifying pollutant releases and by using stream modeling techniques. The potential benefits to human health are evaluated by estimating the potential reduction of carcinogenic risk and non-carcinogenic hazard from consuming contaminated fish or drinking water. Potential human health impacts from fugitive air emissions are projected at low and maximum potential benefit levels using an air dispersion model. Risks to POTW maintenance workers, who may be exposed to pollutants volatilizing from influent wastewaters, are also estimated. In addition, recent literature is reviewed for evidence of documented environmental impacts (e.g., case studies) on aquatic life, human health, and POTW operations and for impacts on the quality of receiving water and ambient air.

The modeling for this analysis was originally performed using the EPA distillation process change as the proposed treatment option. The results of this initial analysis showed limited environmental gains beyond current treatment. Subsequently, steam stripping was selected by EPA as the proposed treatment option. Although distillation is a more effective treatment technology for removing volatile organic compounds than is steam stripping, the overall projected loads from these two treatment technologies are roughly comparable. Therefore, the initial analysis was rerun using the steam stripping pollutant loads only for those facilities for which aquatic life or human health criteria excursions, or POTW inhibition problems were projected at current loadings.

The following sections of this report describe: 1) the methodology used in the evaluation of projected water and air quality impacts for direct and indirect discharging facilities and potential human health risks and benefits (including assumptions and caveats) and in the evaluation of documented environmental impacts; 2) data sources used for evaluating water and air quality impacts such as plant-specific data, information used to evaluate POTW operations, water quality criteria, population and climatologic data, and information used to evaluate human health risks and benefits; 3) a summary of the results of this analysis; and 4) a complete list of references cited in this report. The various appendices presented in Volume II provide additional detail on the specific information addressed in the main report.

2. METHODOLOGY

2.1 Projected Water Quality Impacts

The water quality impacts of pharmaceutical manufacturing discharges are evaluated by comparing projected instream concentrations with ambient water quality criteria,[2] and by estimating the human health risks associated with the consumption of fish and drinking water from waterbodies impacted by the pharmaceutical industry at various treatment options. The methodologies used in this evaluation are described in detail below.

2.1.1 Comparison of Instream Concentrations with Ambient Water Quality Criteria

Current and steam stripping pollutant releases[3] are quantified and compared and potential aquatic life and human health impacts resulting from current and steam stripping pollutant releases are evaluated using stream modeling techniques. Projected instream concentrations for each pollutant are compared to EPA water quality criteria guidance or to toxic effect levels (i.e., lowest reported or estimated toxic concentration) for pollutants for which no EPA water quality criteria guidance has been published. Inhibition of POTW operation and

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[2]In performing this analysis, EPA used guidance documents published by EPA that recommend numeric human health and aquatic life water quality criteria for numerous pollutants. States often consult these guidance documents when adopting water quality criteria as part of their water-quality standards. However, because those State adopted criteria may vary, EPA used the nationwide criteria guidance as the most representative values.

[3]Only pollutants that are proposed for regulation are evaluated (See Section 4.1); however, three pollutants have been removed as candidates since this analysis was completed (glycol ethers, bis(chloromethyl) ether and dimethylcarbamyl chloride). In addition, pollutant loadings at steam stripping treatment levels have been received and modeled since this analysis was initially completed using distillation pollutant loadings. Because the projected loads from these two treatment technologies are roughly comparable, the initial analysis was rerun using the steam stripping pollutant loads only for those facilities for which aquatic life or human health criteria excursions or POTW inhibition problems were projected at current loadings.

sludge contamination are also evaluated. The following three sections describe the methodology and assumptions used for evaluating the impact of direct and indirect discharging facilities.

2.1.1.1 *Direct Discharging Facilities*

Using a stream dilution model that does not account for fate processes, projected instream concentrations are calculated at current and steam stripping treatment levels for stream segments with AC and BD[4] direct discharging facilities. For stream segments with multiple pharmaceutical facilities, pollutant loadings are summed before concentrations are calculated. The dilution model used for estimating instream concentrations is as follows.

$$C_{is} = \frac{L/OD}{FF + SF} \times CF \qquad \text{(Eq. 1)}$$

where:

C_{is}	=	instream pollutant concentration (μg/L)
L	=	facility pollutant loading (lbs/year)
OD	=	facility operation (days/year)
FF	=	facility flow (million gal/day)
SF	=	receiving stream flow (million gal/day)
CF	=	conversion factors for units

The facility-specific data (i.e., pollutant loading, operating days, and facility flow) used in Eq. 1 are derived from various sources as described in Section 3.1.1 of this report. Three receiving stream flow conditions (1Q10 low flow, 7Q10 low flow, and harmonic mean flow) are used for the two treatment technology options. The 1Q10 and 7Q10 flows are the lowest 1-day and the lowest consecutive 7-day average flow during any 10-year period, respectively, and are used to estimate potential acute and chronic aquatic life impacts, respectively, as recommended

[4]AC facilities use fermentation or chemical synthesis processes and BD facilities use extraction, mixing, compounding and formulating processes.

in the *Technical Support Document for Water Quality-based Toxics Control* (U.S. EPA, 1991a). The harmonic mean flow is defined as the reciprocal of the mean value of the reciprocal of individual values and is used to estimate potential human health impacts. EPA recommends the long-term harmonic mean flow as the design flow for assessing potential human health impacts because it provides a more conservative estimate than the arithmetic mean flow. 7Q10 flows are also not appropriate for assessing potential human health impacts because they have no consistent relationship with the long-term mean dilution.

Because stream flows are not available for hydrologically complex waters such as bays, estuaries, and oceans, site-specific critical dilution factors (CDFs) or estuarine dissolved concentration potentials (DCPs) are used to predict pollutant concentrations for facilities discharging to estuaries and bays as follows.

$$C_{es} = \left[\left(\frac{L/OD}{FF} \right) x\ CF \right] / \ CDF \qquad \text{(Eq. 2)}$$

where:

C_{es}	=	estuary pollutant concentration (μg/L)
L	=	facility pollutant loading (lbs/year)
OD	=	facility operation (days/year)
FF	=	facility flow (million gal/day)
CDF	=	critical dilution factor
CF	=	conversion factors for units

$$C_{es} = L\ x\ DCP\ x\ CF \qquad \text{(Eq. 3)}$$

where:

C_{es}	=	estuary pollutant concentration (μg/L)
L	=	facility pollutant loading (lbs/year)
DCP	=	dissolved concentration potential (mg/L)
CF	=	conversion factor for units

Site-specific critical dilution factors are obtained from a survey of States and Regions recently conducted by EPA's Office of Pollution Prevention and Toxics (OPPT) *(Mixing Zone Dilution Factors for New Chemical Exposure Assessments*, draft report, U.S. EPA, 1992a). The Strategic Assessment Branch of the National Oceanic and Atmospheric Administration's (NOAA) Ocean Assessments Division has developed DCPs based on freshwater inflow and salinity gradients to predict pollutant concentrations in each estuary in the National Estuarine Inventory (NEI) Data Atlas. These DCPs are applied to predict concentrations. They do not consider pollutant fate and are designed strictly to simulate concentrations of nonreactive dissolved substances. In addition, the DCPs reflect the predicted estuary-wide response and may not be indicative of site-specific locations.

Water quality excursions are determined by dividing the projected instream (Eq. 1) or estuary (Eq. 2 and Eq. 3) pollutant concentrations by EPA ambient water quality criteria or toxic effect levels. A value greater than 1.0 indicates an excursion.

2.1.1.2 *Indirect Discharging Facilities*

(a) Water Quality Impacts

A stream dilution model is used to project receiving stream impacts resulting from releases by AC and BD indirect discharging facilities as shown in Eq. 4. For stream segments with multiple pharmaceutical facilities, pollutant loadings are summed before concentrations are calculated. The facility-specific data used in Eq. 4 are derived from various sources as described in Section 3.1.1 of this report. Three receiving stream flow conditions (1Q10 low flow, 7Q10 low flow, and harmonic mean flow) are used for the two treatment technology options. Pollutant concentrations are predicted for POTWs located on bays and estuaries using site-specific CDFs or NOAA's DCP calculations (Eq. 5 and Eq. 6).

$$C_{is} = (L/OD) \times \frac{(1-TMT) \times CF}{PF + SF} \qquad \text{(Eq. 4)}$$

where:

C_{is}	=	instream pollutant concentration (μg/L)
L	=	facility pollutant loading (lbs/year)
OD	=	facility operation (days/year)
TMT	=	POTW treatment removal efficiency
PF	=	POTW flow (million gal/day)
SF	=	receiving stream flow (million gal/day)
CF	=	conversion factors for units

$$C_{es} = \left[\left(\frac{L/OD \times (1-TMT)}{FF} \right) \times CF \right] / CDF \qquad \text{(Eq. 5)}$$

where:

C_{es}	=	estuary pollutant concentration (μg/L)
L	=	facility pollutant loading (lbs/year)
OD	=	facility operation (days/year)
TMT	=	POTW treatment removal efficiency
PF	=	POTW flow (million gal/day)
CDF	=	critical dilution factor
CF	=	conversion factors for units

$$C_{es} = L \times (1-TMT) \times DCP \times CF \qquad \text{(Eq. 6)}$$

where:

C_{es}	=	estuary pollutant concentration (μg/L)
L	=	facility pollutant loading (lbs/year)
TMT	=	POTW treatment removal efficiency
DCP	=	dissolved concentration potential (mg/L)
CF	=	conversion factors for units

Impacts are determined by comparing projected instream pollutant concentrations (Eq. 4) at reported POTW flows and at 1Q10 low, 7Q10 low, and harmonic mean receiving stream flows with EPA water quality criteria or toxic effect levels for the protection of aquatic life and human health (see Section 2.1.1.1 for discussion on receiving stream flows); projected estuary pollutant concentrations (Eq. 5 and Eq. 6), based on CDFs or DCPs, are compared to EPA water quality criteria or toxic effect levels to determine impacts. Water quality criteria excursions are determined by dividing the projected instream or estuary pollutant concentration by the EPA water quality criteria or toxic effect levels. A value greater than 1.0 indicates an excursion.

(b) Impacts on POTWs

Impacts on POTW operations are calculated in terms of inhibition of POTW processes (i.e., inhibition of microbial degradation) and contamination of POTW sludges. Inhibition of POTW operations is determined by dividing calculated POTW influent levels (Eq. 7) with chemical-specific inhibition threshold levels. Excursions are indicated by a value greater than 1.0.

$$C_{pi} = \frac{L/OD}{PF} \times CF \qquad \text{(Eq. 7)}$$

where:

C_{pi}	=	POTW influent concentration (μg/L)
L	=	facility pollutant loading (lbs/year)
OD	=	facility operation (days)
PF	=	POTW flow (million gal/day)
CF	=	conversion factors for units

Contamination of sludge (thereby limiting its use for land application, etc.) is evaluated by dividing projected pollutant concentrations in sludge (Eq. 8) by available EPA-developed criteria values for sludge. A value greater than 1.0 indicates an excursion.

$$C_{SP} = (L/OD) \times TMT \times PART \times SGF \times CF \qquad \text{(Eq. 8)}$$

where:

C_{sp}	=	sludge pollutant concentration (mg/kg)
L	=	facility pollutant loading (lbs/year)
OD	=	facility operation (days/year)
TMT	=	POTW treatment removal efficiency
PART	=	chemical-specific sludge partition factor
SGF	=	sludge generation factor (5.96 ppm)
CF	=	conversion factors for units.

Facility-specific data and information used to evaluate POTWs are derived from the sources described in Sections 3.1.1 and 3.1.2. For facilities that discharge to the same POTW, their individual loadings are summed before the POTW influent and sludge concentrations are calculated.

The partition factor is a measure of the tendency for the pollutant to partition in sludge when it is removed from wastewater. For predicting sludge generation, the model assumes that 1,400 pounds of sludge are generated for each million gallons of wastewater processed (Metcalf & Eddy, 1972). This results in a sludge generation factor of 5.96 (that is, for every 1 ppb of pollutant removed from wastewater and partitioned to sludge, the concentration in sludge is 5.96 ppm dry weight).

2.1.1.3 *Assumptions and Caveats*

The following assumptions are used in this analysis:

- Background concentrations of each pollutant, both in the receiving stream and in the POTW influent, are equal to zero; therefore, only the impacts of discharging facilities are evaluated. (This assumption may result in an overly conservative assessment of environmental benefits regarding the frequency of water quality standards exceedance.)

- An exposure duration of 365 days is used to determine the likelihood of actual excursions of human health criteria or toxic effect levels.

- Complete mixing of discharge flow and stream flow occurs across the stream at the discharge point. This mixing results in the calculation of an "average stream" concentration even though the actual concentration may vary across the width and depth of the stream.

- The process water at each facility and the water discharged to a POTW are obtained from a source other than the receiving stream.

- The pollutant load to the receiving stream is assumed to be continuous and is assumed to be representative of long-term facility operations. This assumption may overestimate risks to human health and aquatic life.

- 1Q10 and 7Q10 receiving stream flow rates are used to estimate aquatic life impacts, and harmonic mean flow rates are used to estimate human health impacts. 1Q10 low flows are estimated using the results of a regression analysis conducted by Versar for EPA's Office of Pollution Prevention and Toxics (OPPT) of 1Q10 and 7Q10 flows from representative U.S. rivers and streams (*Upgrade of Flow Statistics Used to Estimate Surface Water Chemical Concentrations for Aquatic and Human Exposure Assessment,* Versar, 1992). Harmonic mean flows are estimated from the mean and 7Q10 flows as recommended in the *Technical Support Document for Water-Quality-based Toxics Control* (U.S. EPA, 1991a). These flows may not be the same as those used by specific states to assess impacts.

- Pollutant fate processes such as sediment adsorption, volatilization, and hydrolysis are not considered. This may result in estimated instream concentrations that are environmentally conservative (higher).

- Pollutants without a specific POTW treatment removal efficiency, provided by EPA or found in the literature are assigned a removal efficiency of zero; pollutants without a specific partition factor are assigned a value of zero.

- Water quality criteria or toxic effect levels developed for freshwater organisms are used in the analysis of facilities discharging to estuaries or bays.

- Of those facilities reporting a wastewater discharge, the number of facilities modeled was limited by available data on receiving streams and POTWs.

2.1.2 Estimation of Human Health Risks and Benefits

The potential benefits to human health are evaluated by estimating the risks (carcinogenic and systemic effects) associated with reducing pollutant levels in fish tissue and drinking water from current to steam stripping treatment levels.[5] The following three sections describe the methodology and assumptions used for evaluating the human health risks from the consumption of fish tissue and drinking water derived from water bodies impacted by AC and BD direct and indirect discharging facilities.

2.1.2.1 *Fish Tissue*

To determine the potential benefits, in terms of reduced cancer cases, associated with reducing levels in fish tissue, lifetime average daily doses (LADD) and individual risk levels are estimated for each pollutant discharged from a facility based on the instream pollutant concentrations calculated at current and steam stripping treatment levels in the site-specific stream dilution analysis (see Section 2.1.1). Estimates are presented for sport fishermen, subsistence fishermen and the general population. LADDs are calculated as follows.

$$LADD = (C \times IR \times BCF \times F \times D) / (BW \times LT) \qquad \text{(Eq. 9)}$$

where:

LADD	=	potential lifetime average daily dose (mg/kg/day)
C	=	exposure concentration (mg/L)

[5]Since no substantial risks are projected at current treatment levels, i.e., the highest wasteload, the analysis was not rerun for steam stripping. Distillation treatment levels are used in the analysis.

IR	=	ingestion rate (see Section 2.1.2.3 - Assumptions)
BCF	=	bioconcentration factor, l/kg (whole body x 0.5)
F	=	frequency duration (365 days/year)
D	=	exposure duration (70 years)
BW	=	body weight (70 kg)
LT	=	lifetime (70 years x 365 days/year)

Individual risks are calculated as follows:

$$R = LADD \times SF \qquad \text{(Eq. 10)}$$

where:

R	=	individual risk level
SF	=	potency slope factor $(mg/kg\text{-}day)^{-1}$

The estimated individual pollutant risk levels are then applied to the potentially exposed populations of sport fishermen, subsistence fishermen, and the general population to estimate the potential number of excess annual cancer cases occurring over the life of the population. The number of excess cancer cases is then summed on a pollutant, facility, and overall industry basis. The number of reduced cancer cases are assumed to be the difference between the estimated risks at current and steam stripping/distillation treatment levels.

Potential reductions in risks due to reproductive, developmental, or other chronic and subchronic toxic effects are estimated by comparing the estimated average daily dose and the oral reference dose (RfD) for a given chemical pollutant as follows:

$$HQ = ORI/RfD \qquad \text{(Eq. 11)}$$

where:

HQ	=	hazard quotient

ORI	=	oral intake (LADD x BW, mg/day)
RfD	=	reference dose (mg/day assuming a body weight of 70 kg)

A hazard index (i.e., sum of individual pollutant hazard quotients) is then calculated for each facility or receiving stream. A hazard index greater than 1.0 indicates that toxic effects may occur in exposed populations. The size of the subpopulations affected are summed and compared at the various treatment levels to assess benefits in terms of reduced systemic toxicity.

2.1.2.2 *Drinking Water*

Potential benefits associated with reducing levels in drinking water are determined in a similar manner. LADDs for drinking water consumption are calculated as follows:

$$LADD = (C \times IR \times F \times D) / (BW \times LT) \qquad \text{(Eq. 12)}$$

where:

LADD	=	potential lifetime average daily dose (mg/kg/day)
C	=	exposure concentration (mg/L)
IR	=	ingestion rate (2L/day)
F	=	frequency duration (365 days/year)
D	=	exposure duration (70 years)
BW	=	body weight (70 kg)
LT	=	lifetime (70 years x 365 days/year)

Estimated individual pollutant risk levels greater than 10^{-6} are applied to the population served downstream by any drinking water utilities within 50 miles from each discharge site to determine the number of excess annual cancer cases that may occur during the life of the population. Systemic toxicant effects are evaluated by estimating the sizes of populations exposed to pollutants from a given facility the sum of whose individual hazard quotients yields a hazard index (HI) greater than 1.0.

2.1.2.3 *Assumptions and Caveats*

The following assumptions are used in the human health risks and benefits analysis.

- A linear relationship is assumed between pollutant loading reductions and benefits attributed to the clean-up of surface waters.

- Synergistic effects of multiple chemicals on aquatic ecosystems are not assessed. Therefore, the total benefit of reducing toxics may be underestimated.

- The total number of persons who might consume recreationally caught fish and the number that rely upon fish on a subsistence basis in each State is estimated, in part, by assuming that these fishermen regularly share their catch with family members. Therefore, the number of fishermen in each State is multiplied by the average household size in each State. The remainder of the population of these states is assumed to be the "general population" consuming commercially caught fish.

- Five percent of the resident fishermen in a given State are assumed to be subsistence fishermen. The other 95 percent are assumed to be sport fishermen.

- Commercially or recreationally valuable species are assumed to occur or be taken in the vicinity of the discharges included in the evaluation.

- Ingestion rates of 6.5 grams per day for the general population, 30 grams per day (30 years) + 6.5 grams per day (40 years) for sport fishermen, and 140 grams per day for subsistence fishermen are used in the analysis of fish tissue (*Exposure Factors Handbook*, U.S. EPA, 1989a)

- All rivers or estuaries within a State are equally fished by any of that state's resident fishermen and the fish consumed only by the population within that State.

- Populations potentially exposed to discharges to rivers or estuaries that border more than one State are estimated based only on populations within the State in which the facility is located.

- The size of the population potentially exposed to fish caught in an impacted water body in a given State is estimated based on the ratio of impacted river miles to total river miles in that State or impacted estuary square miles to total estuary square miles in that State. The number of miles potentially impacted by a facility's discharge is assumed to be 50 miles for rivers and the total surface area of the various estuarine zones for estuaries.

- Pollutant fate processes (e.g., sediment adsorption, volatilization, hydrolysis) are not considered in estimating the concentration in drinking water or fish; consequently, estimated concentrations are environmentally conservative (higher).

2.2 Projected Air Quality Impacts

Many of the chemicals released by pharmaceutical manufacturing facilities can exhibit human health toxicity via the inhalation exposure route. A two-part approach is used to assess environmental impacts from air emissions associated with pharmaceutical treatment options, particularly those which include steam stripping. The first part assesses potential risks to the general public from on-site fugitive emissions from open-air biological treatment using EPA's Graphical Exposure Modeling System (GEMS) Atmospheric Modeling Subsystem (GAMS). GAMS includes the Industrial Source Complex Long Term (ISCLT) air dispersion model linked to site-specific weather and population data. The second part assesses potential risks to POTW maintenance workers from occupational exposures to a toxic mixture of gases partitioning from influent wastewater. The POTW occupational exposure analysis is based on the procedure presented in *Guidance to Protect POTW Workers from Toxic and Reactive Gases and Vapors* (U.S. EPA, 1992b).

2.2.1 Estimation of Human Health Risks and Benefits (Fugitive Air Emissions)

Pharmaceutical manufacturers use and release several volatile organic compounds that exhibit carcinogenic and/or systemic health effects on humans and/or laboratory animals. In the near-ground atmosphere, these chemicals may pose a threat to human health via inhalation. Inhalation exposures can be quantitatively assessed using air dispersion models, information on the location and source of release, mass release amounts, and population density. For the purposes of this analysis, the exposed population is assumed to be the general public living in the vicinity of the point of release.

Two sets of fugitive emissions from on-site treatment are examined:

- Data provided by industry that represent the "low estimate" of releases; and
- Data generated by EPA OST/EAD that represent the "maximum estimate" of releases.

The "low estimate" data are compiled from responses to the CWA Section 308 Pharmaceutical Questionnaire. The "low estimate" benefits of steam stripping are estimated by assuming that this process will remove all volatile pollutants from air emissions.

The "maximum estimate" data are compiled from engineering estimates (December 1994 loading data) based on the WATER7 wastewater treatment model and a mass balance approach to examining wastewater levels prior to treatment and current end of pipe releases. The "maximum estimate" represents the upper boundary of potential air emissions of volatile organic compounds from pharmaceutical manufacturing processes.

2.2.1.1 *Preliminary Screening*

In GAMS, site-specific air modeling is an iterative process implemented on a facility-specific, pollutant-specific basis. A screening procedure is used to eliminate facility-pollutant release combinations which result in potential exposures that are small compared to their toxic effect level. The screening procedure involves calculating a hazard ratio (HAZ) based on maximum potential concentration exposure. HAZ is the maximum potential downwind concentration (MAX) divided by the lowest level of concern concentration (LOC) as follows:

$$HAZ = \left(\frac{MAX}{LOC} \right) \qquad \text{(Eq. 13)}$$

Facility-pollutant release combinations where HAZ < 1.0 are dropped from further analysis because the chemical concentration is highly unlikely to reach a level of concern at any location in the vicinity of the facility. The remaining facility-pollutant release combinations proceed to the next level of air modeling. The greater the value for HAZ the greater the likelihood of harmful human health exposure.

The maximum potential downwind concentration is calculated using a Gaussian plume dispersion equation for annual average concentration presented in the *Workbook of Atmospheric Dispersion Estimates* (Turner, 1970). The maximum average annual downwind concentration equation is:

$$MAX = f(\theta) \; x \; \frac{2.03 \; x \; Q \; x \; CF_1 \; x \; CF_2}{X \; x \; s \; x \; u} \; e^{\left[-0.5 \; x \left(\frac{H}{s} \right)^2 \right]} \qquad \text{(Eq. 14)}$$

where,

MAX	=	Maximum average annual downwind concentration (mg/m^3)
2.03	=	Aggregation of constants (unitless)
$f(\theta)$	=	Fraction of the year the wind is from direction θ (unitless) = 0.15
Q	=	Annual loading (lbs/year)
CF_1	=	Conversion factor of 4.53E+5 mg/lb
CF_2	=	Conversion factor of 3.17E-8 yr/sec
X	=	Downwind distance where maximum concentration occurs (m) = 40.55
s	=	Vertical dispersion coefficient (m) = 2.12
u	=	Mean wind speed (m/sec) = 5.5
H	=	Release height (m) = 3

The parameter input values are selected to achieve a maximum potential concentration using reasonable assumptions for release height, fraction of the year wind blows from one direction, and wind speed; and further assuming stable atmospheric conditions, which will dominate in the long-term. Use of this equation is conservative because it is intended to be

applied to stack releases, which tend to have more concentrated plumes than the area source releases considered here.

The LOC concentrations are compiled from the following sources:

- EPA unit risks (UR) for cancer at a 10^{-6} risk level, or EPA reference concentrations (RfC) from the Integrated Risk Information System (IRIS) or the Health Effects Assessment Summary Tables (HEAST),
- American Council of Governmental and Industrial Hygienists (ACGIH) Threshold Limit Values (TLV), and
- Occupational Safety and Health Administration (OSHA) permissible exposure limits (PEL).

2.2.1.2 *Atmospheric Dispersion Modeling*

More complex atmospheric modeling analysis is performed on those facility-pollutant releases identified in the screening procedure using HAZ scores. Site-specific modeling analysis is used to predict potential atmospheric concentrations from fugitive releases and assess the potential impact to the surrounding population.

The Industrial Source Complex Long Term (ISCLT) model is used in modeling atmospheric dispersion. ISCLT is an EPA-supported gaussian plume air dispersion model that is incorporated within the Office of Pollution Prevention and Toxics (OPPT) Graphical Exposure Modeling System (GEMS) Atmospheric Modeling Subsystem (GAMS). In GAMS, the ISCLT algorithms can run with site-specific atmospheric profile and U.S. Census population data inputs. GAMS requires location identifiers such as latitude and longitude or ZIP code, and locates the nearest STability ARray (STAR) weather data (usually airports). The STAR data are used to predict the pollutant concentration in 16 sectors around concentric rings surrounding the point of release. These concentrations are then linked with U.S Census data at the block group/enumeration district (BG/ED) level to estimate exposure levels and excess annual cancer

cases. Additional information concerning the ISCLT model and the GAMS system may be found in *Industrial Source Complex (ISC) Dispersion Model User's Guide - Second Edition (Revised)* (U.S. EPA, 1987a), and *GAMS Version 3.0 - User's Guide* (U.S. EPA, 1990a).

Input data for ISCLT are obtained through user input (site- and pollutant-specific data) or from GAMS via STAR stations (based on the user-supplied information). The GAMS menu driven system allows the user to select EPA regulatory defaults or input-specific parameters for detailed analysis. Latitude and longitude coordinates are obtained from either 308 Questionnaire responses or the Toxic Release Inventory System (TRIS), and a standard polar receptor grid is used. The receptor (breathing individual) is assumed to be at ground level, inhale 20 m^3/day, and weigh 70 kilograms (standard adult exposure factors).

Volatilization (fugitive emissions) from water treatment is modeled as an area source release based on ISCLT equations (U.S. EPA, 1987a). The area of release is determined by selecting parameters provided in the 308 Questionnaire based on the following hierarchy: (1) the smallest equalization tank, (2) the smallest other tank (including stabilization and neutralization), or (3) the average equalization tank reported in the 308 Questionnaire (4973 ft^2). GAMS requires input of side dimension only (in meters). Therefore, all treatment units are assumed to be square.

2.2.1.3 *Risk Calculations*

ISCLT model results for each facility are run though the GAMS Exposure and Risk Estimation (GAMSERE) procedure (U.S. EPA, 1990a) to generate Lifetime Average Daily Doses (LADDs) associated with BG/ED populations and the number of excess cancer cases over background levels. The LADD for inhalation used in the GAMSERE procedure is given as:

$$LADD = (CONC \times CF \times IR) / BW \qquad \text{(Eq. 15)}$$

where,

LADD	=	potential lifetime average daily dose (mg/kg/day)
CONC	=	annual average concentration estimate (ug/m^3)
IR	=	daily inhalation rate (20 m^3/day)
CF	=	conversion factor (0.001 mg/μg)
BW	=	body weight (70 kg)

The LADD value is used to evaluate exposure for both systemic and carcinogenic pollutants. Systemic pollutant LADD values are compared in GAMSERE to reference dose values to estimate the population exposed to levels exceeding the reference dose. The cumulative population exposed to greater than the reference dose are reported by BG/ED units. Excess cancer risk over background is calculated using the a potency slope factor or a unit risk factor. To estimate excess annual cancer risk, GAMSERE uses the following equation:

$$RISK = LADD \times SF \qquad \text{(Eq. 16)}$$

where,

RISK	=	lifetime excess risk over background
LADD	=	potential lifetime average daily dose (mg/kg/day)
SF	=	potency slope factor (mg/kg/day)$^{-1}$

2.2.2 Estimation of POTW Occupational Risks and Benefits

Occupational exposure at POTWs is modeled based on the mixture of toxic vapors that may partition out of the influent water into the surrounding air. POTW workers constitute the potentially exposed population for this analysis. This analysis does not consider sewer workers because they presumably will not be exposed to toxic vapors for long periods without utilizing protective gear.

EPA developed guidance presented in *Guidance to Protect POTW Workers from Toxic and Reactive Gases and Vapors* (U.S. EPA, 1992b) to screen industrial discharges for potential

adverse effects on POTW workers. The general procedure for predicting the potential vapor HAZARD associated with the discharge of a mixture of volatile organic compounds (U.S. EPA, 1992b) includes the following steps:

1. Determine pollutant concentrations (mg/L) in wastewater.

2. Obtain 8 hour/day, 40 hours/week time weighted average ACGIH Threshold Limit Values (TLV) in units of mg/m^3 for pollutants.

3. Convert aqueous phase pollutant concentration (mg/L) to vapor phase pollutant concentrations (mg/m^3) in surrounding air using chemical-specific Henry's Law Constants in the appropriate units as follows.

$$C_v = H_c \, x \, C_a \qquad \text{(Eq. 17)}$$

where:

C_v = Vapor phase pollutant concentration (mg/m^3)
H_c = Henry's Law Constant (mg/m^3)/(mg/L)
C_a = Aqueous phase pollutant concentration (mg/L)

4. Calculate the hazard ratio for a given pollutant by dividing the threshold concentration (i.e., TLV) identified in Step 2 by the predicted concentration from Step 3.

5. Sum the hazard ratios for all pollutants at the POTW.

6. Identify those POTW facilities with sum hazard ratios > 1, indicating potential adverse health impacts.

This methodology assumes that equilibrium conditions exist, that Henry's Law Constant is a good indicator of air-wastewater partitioning, and that the toxic effects indicated by TLVs are additive across pollutants. In addition, there are a number of general assumptions based on the definition of an "average worker". The "average worker" is assumed to weigh 70 kilograms, work 40 hours per week, and be in good health. POTW effluent flow, obtained

from the NEEDS Survey, is used as a surrogate for influent flow to dilute pollutant load estimates for the wastewater concentration calculation.

2.2.3 Assumptions and Caveats

The following assumptions are made in the air quality analysis. Many are included in the previous text of Section 2.2 for necessary clarification and are listed in this section as a summary.

- The maximum average annual downwind concentration equation (i.e., Eq. 14) is assumed to be conservative as it is intended to be applied to stack releases, which tend to have more concentrated plumes than the area source releases considered in this analysis.

- If a treatment option that includes steam stripping is selected, significant fugitive air emissions will not occur.

- The screening procedure equation to calculate maximum average annual downwind concentration assumes the following parameter default values:

  - Fraction of the year the wind is from direction $f(\theta) = 0.15$;
  - Downwind distance for maximum concentration (X) = 40.55 m;
  - Vertical dispersion coefficient (s) = 2.12 m;
  - Mean wind speed (u) = 5.5 m/sec;
  - Release height (H) = 3 m.

- The exposed population is the general public living in the vicinity of the point of release and encompassed by the standard polar grid generated in the GAMS analysis.

- Atmospheric conditions used in the ISCLT model are based on long-term average values and are, therefore, assumed to be stable under the assumptions used in the model development.

- No chemical decay rate is employed in the GAMS model. It is assumed that at these release amounts, dispersion will likely dilute chemical concentrations to levels far below concern prior to any significant photooxidation or scavenging.

- The receptor (breathing individual) is assumed to be at ground level, inhale 20 m^3/day, and weigh 70 kilograms (standard adult exposure factors).

- The screening procedure is assumed to be a reasonable method limiting detailed analysis to those releases most likely to adversely effect the surrounding population.

- Open area for equalization tanks and stabilization ponds are provided by EPA's 308 questionnaire. Facilities without this data are assigned the average equalization tank area for those facilities that did report tank areas.

- In the POTW occupational exposure analysis, it is assumed that equilibrium conditions exist, that Henry's Law Constant is a good indicator of air-wastewater partitioning, and that the toxic effects indicated by TLVs are additive across pollutants.

- POTW effluent flow, obtained from the NEEDS Survey, is used as a surrogate for influent flow to dilute pollutant load estimates for the wastewater concentration calculation.

- The POTW occupational exposure analysis (U.S. EPA, 1992b) assumes that an "average worker":

  - is exposed to the pollutant throughout their occupational lifetime - ages 18 to 65;
  - works a 40-hour week;
  - weighs 70 kilograms;
  - is healthy, with no prior physical or health deficiencies; and
  - has a normal respiration rate.

- The POTW occupational exposure analysis requires the following simplifying assumptions for the use of Henry's Law Constant to conditions in the sewer line:

  - The wastewater and air temperatures at the POTW are approximately 25 degrees Celsius.

  - The presence of other constituents within the wastewater have no synergistic or antagonistic effect on the volatilization of any given pollutant.

  - The screening approach assumes that the air flow above the POTW unit operations is negligible, thereby, allowing equilibrium conditions to be approximated in the headspace above the unit operations.

  - The screening approach assumes instantaneous attainment of vapor-liquid equilibrium and does not consider volatilization rates.

- The POTW occupational exposure analysis assumes that the toxic effects of the pollutants in the mixture are additive. Therefore, hazard quotients are also additive when calculating the POTW exposure.

2.3 Documented Environmental Impacts

Published literature and survey data have been reviewed for evidence of documented environmental impacts on aquatic life, human health, POTW operations, and the quality of receiving water due to discharges of pollutants from pharmaceutical manufacturing. Reported impacts on the environment and biota/effect are compiled and summarized for various studies and are presented by study site and facility.

3. DATA SOURCES

3.1 Water Quality Impacts

Readily available EPA and other agency databases, models and reports are used in the evaluation of water quality impacts. The following four sections describe the various data sources used in the analysis.

3.1.1 Facility-Specific Data

Projected pharmaceutical facility effluent process flows and distillation pollutant loadings (Appendix A) are obtained from the Engineering and Analysis Division (EAD) (March/April 1994). Pollutant loadings based on steam stripping were received from EAD in December 1994.

The locations of pharmaceutical manufacturing facilities on receiving streams are identified using USGS cataloging and stream segment (reach) numbers contained in EPA's Industrial Facilities Discharge (IFD) data base. Latitude/longitude coordinates, if available, are used to locate those facilities and POTWs that have not been assigned a reach number in IFD. The names, locations, and the flow data for the POTWs to which the indirect facilities discharge are obtained from the Pharmaceutical 308 Questionnaire, EPA's 1992 NEEDS Survey, IFD, and EPA's Permit Compliance System (PCS).

The receiving stream flow data are obtained from either the W.E. Gates study data or from measured streamflow data, both of which are contained in EPA's GAGE file. The W.E. Gates study contains calculated average and low flow statistics based on the best available flow data and on drainage areas for reaches throughout the United States. The GAGE file also includes average and low flow statistics based on measured data from USGS gaging stations. "Dissolved Concentration Potentials (DCPs)" for estuaries and bays are obtained from the Strategic Assessment Branch of NOAA's Ocean Assessments Division (Appendix B). Critical

Dilution Factors are obtained from the *Mixing Zone Dilution Factors for New Chemical Exposure Assessments* (U.S. EPA, 1992a).

3.1.2 Information Used to Evaluate POTW Operations

POTW treatment efficiency removal rates are developed from POTW removal data and pilot-plant studies or by using the removal rate of a similar pollutant when data are not available (Appendix C). Use of the selected removal rates assumes that the evaluated POTWs are well-operated and have at least secondary treatment in place. Sources of data include *POTW Pass-Through Analysis for the Pharmaceutical Industry* (U.S. EPA, 1993a), EPA's Risk Reduction Engineering Laboratory (RREL) Treatability Database, and the *Development Document for Effluent Limitations Guidelines and Standards for the Organic Chemicals, Plastics and Synthetic Fibers Point Source Category* (U.S. EPA, 1987b).

Inhibition values are obtained from *Guidance Manual for Preventing Interference at POTWs* (U.S. EPA, 1987c) and from *CERCLA Site Discharges to POTWs: Guidance Manual* (U.S. EPA, 1990b). The most conservative values for activated sludge are used. For pollutants with no specific inhibition value, a value based on compound type (e.g., aromatics) is used.

Sewage sludge regulatory levels, if available for the pollutants of concern, are obtained from the Federal Register 40 CFR Part 503, Standards for the Use or Disposal of Sewage Sludge, Final Rules (February 19, 1993). Pollutant limits established for the final use or disposal of sewage sludge when the sewage sludge is applied to agricultural and non-agricultural land are used (Appendix C). Sludge partition factors are obtained from the *Report to Congress on the Discharge of Hazardous Wastes to Publicly-Owned Treatment Works (Domestic Sewage Study)* (U.S. EPA, 1986).

3.1.3 Water Quality Criteria (WQC)

The ambient criteria (or toxic effect levels) for the protection of aquatic life and human health are obtained from a variety of sources including EPA criteria guidance documents, EPA's Assessment Tools for the Evaluation of Risk (ASTER), and EPA's Integrated Risk Information System (IRIS) (Appendix C). Ecological toxicity estimations are used when published values are not available. The hierarchies used to select the appropriate aquatic life and human health values are described in the following sections.

3.1.3.1 *Aquatic Life*

Water quality criteria guidance documents for many pollutants have been published by EPA for the protection of freshwater aquatic life (acute and chronic criteria). States often consult these guidance documents when adopting numeric water quality criteria as part of their water quality standards. The acute value represents a maximum allowable 1-hour average concentration of a pollutant at any time and can be related to acute toxic effects on aquatic life. The chronic value represents the average allowable concentration of a toxic pollutant over a 4-day period at which a diverse genera of aquatic organisms and their uses should not be unacceptably affected, provided that these levels are not exceeded more than once every 3 years.

EPA has used EPA criteria guidance documents as one source for projecting potential water quality impacts of the proposed rule. For pollutants for which no numeric water quality criteria guidance has been published, specific toxicity values (acute and chronic effect concentrations reported in published literature or estimated using various application techniques) are used. In selecting values from the literature, measured concentrations from flow-through studies under typical pH and temperature conditions are preferred. The test organism must be a North American resident species of fish or invertebrate. The hierarchies used to select the appropriate acute and chronic values are listed below in descending order of priority.

Acute Aquatic Life Values:

- National acute freshwater quality criteria;
- Lowest reported acute test values (96-hour LC_{50} for fish and 48-hour EC_{50}/LC_{50} for daphnids);
- Lowest reported LC_{50} test value of shorter duration, adjusted to estimate a 96-hour exposure period;
- Lowest reported LC_{50} test value of longer duration, up to a maximum of two weeks exposure; and
- Estimated 96-hour LC_{50} from the ASTER QSAR model.

Chronic Aquatic Life Values:

- National chronic freshwater quality criteria;
- Lowest reported maximum allowable toxic concentration (MATC), lowest observable effect concentration (LOEC), or no observable effect concentration (NOEC);
- Lowest reported chronic growth or reproductive toxicity test concentration;
- Estimated chronic toxicity concentration from a measured acute chronic ratio for a less sensitive species, quantitative structure activity relationship (QSAR) model, or default acute:chronic ratio of 10:1.

3.1.3.2 *Human Health*

Water quality criteria for the protection of human health are established in terms of a pollutant's toxic effects, including carcinogenic potential. These human health criteria values are developed for two exposure routes: (1) ingesting the pollutant via contaminated aquatic organisms only, and (2) ingesting the pollutant via both water and contaminated aquatic organisms as follows.

For Toxicity Protection (ingestion of organisms only)

$$HH_{oo} = \frac{RfD \times CF}{IR_f \times BCF} \qquad \text{(Eq. 18)}$$

where:

HH_{oo}	=	human health value (μg/L)
RfD	=	reference dose for a 70-kg individual (mg/day)
IR_f	=	fish ingestion rate (0.0065 kg/day)
BCF	=	bioconcentration factor (liters/kg)
CF	=	conversion factor for units (1,000 μg/mg)

For Carcinogenic Protection (ingestion of organisms only)

$$HH_{oo} = \frac{BW \times RL \times CF}{SF \times IR \times BCF} \qquad \text{(Eq. 19)}$$

where:

HH_{oo}	=	human health value (μg/L)
BW	=	body weight (70 kg)
RL	=	risk level (10^{-6})
SF	=	cancer slope factor $(mg/kg/day)^{-1}$
IR_f	=	fish ingestion rate (0.0065 kg/day)
BCF	=	bioconcentration factor (liters/kg)
CF	=	conversion factor for units (1,000 μg/mg)

For Toxicity Protection (ingestion of water and organisms)

$$HH_{wo} = \frac{RfD \times CF}{IR_w + IR_f} \qquad \text{(Eq. 20)}$$

where:

HH_{wo} = human health value (μg/L)
RfD = reference dose for a 70-kg individual (mg/day)
IR_w = water ingestion rate (2 liters/day)
IR_f = fish ingestion rate (0.0065 kg/day)
BCF = bioconcentration factor (liters/kg)
CF = conversion factor for units (1000 μg/mg)

For Carcinogenic Protection (ingestion of water and organisms)

$$HH_{wo} = \frac{BW \times RL \times CF}{SF \times IR_w + IR_f \times BCF} \qquad \text{(Eq. 21)}$$

where:

HH_{wo} = human health value (μg/L)
BW = body weight (70 kg)
RL = risk level (10^{-6})
SF = cancer slope factor $(mg/kg/day)^{-1}$
IR_w = water ingestion rate (2 liters/day)
IR_f = fish ingestion rate (0.0065 kg/day)
BCF = bioconcentration factor (liters/kg)
CF = conversion factor for units (1,000 μg/mg)

The values for ingesting water and organisms are derived by assuming an average daily ingestion of 2 liters of water, an average daily fish consumption rate of 6.5 grams of potentially contaminated fish products, and an average adult body weight of 70 kilograms (*Technical Support Document for Water Quality-Based Toxics Controls* (U.S. EPA, 1991a). Values protective of carcinogenicity are used to assess the potential effects on human health, if EPA has established a slope factor.

Protective concentration levels for carcinogens are developed in terms of non-threshold lifetime risk level. Criteria at a risk level of 10^{-6} are chosen for this analysis. This risk level indicates a probability of one additional case of cancer for every 1,000,000 persons exposed.

Toxic effects criteria for noncarcinogens include systemic effects (e.g., reproductive, immunological, neurological, circulatory, or respiratory toxicity), organ-specific toxicity, developmental toxicity, mutagenesis, and lethality.

The hierarchy used to select the most appropriate human health criteria values is listed below in descending order of priority:

- Calculated human health criteria values using EPA's Integrated Risk Information System (IRIS) reference doses (RfDs) or slope factors (SFs) used in conjunction with adjusted 3 percent lipid BCF values derived from *Ambient Water Quality Criteria Documents* (U.S. EPA, 1980); three percent is the mean lipid content of fish tissue reported in the study from which the average daily fish consumption rate of 6.5g/day was derived;

- Calculated human health criteria values using current IRIS RfDs or SFs and representative BCF values for common North American species of fish or invertebrates or estimated BCF values;

- Calculated human health criteria values using RfDs or SFs from EPA's Health Effects Assessment Summary Tables (HEAST) used in conjunction with adjusted 3 percent lipid BCF values derived from *Ambient Water Quality Criteria Documents* (U.S. EPA, 1980);

- Calculated human health criteria values using current RfDs or SFs from HEAST and representative BCF values for common North American species of fish or invertebrates or estimated BCF values;

- Criteria from the *Ambient Water Quality Criteria Documents* (U.S. EPA, 1980); and

- Calculated human health values using RfDs or SFs from data sources other than IRIS.

This hierarchy is based on Section 2.4.6 of the *Technical Support Document for Water Quality-based Toxics Control* (U.S. EPA, 1991A), which recommends using the most current risk information from IRIS when estimating human health risks. In cases where chemicals have both RfDs and SFs from the same level of the hierarchy, human health values are calculated

using the formulas for carcinogenicity, which always results in the more stringent value of the two given the risk levels employed.

3.1.4 Information Used to Evaluate Human Health Risks and Benefits

Fish ingestion rates for sport fishermen, subsistence fishermen and the general population are obtained from the *Exposure Factors Handbook* (U.S. EPA, 1989a). State population data and average household size are obtained from the 1992 *Statistical Abstract of the United States* (U.S. Bureau of the Census, 1992). Data concerning the number of fishermen in each state (i.e., resident fishermen) are obtained from the 1985 *National Survey of Fishing, Hunting, and Wildlife Associated Recreation* (U.S. FWS, 1985). The total number of river miles or estuary square miles within a state is obtained from the 1990 *National Water Quality Inventory - Report to Congress* (U.S. EPA, 1990c). Drinking water utilities located within 50 miles downstream from each discharge site are identified using EPA's PATHSCAN. The population served by a drinking water utility is obtained from EPA's Drinking Water Supply Files or Federal Reporting Data System. Information used in the evaluation is presented in Appendix D.

3.2 Air Quality Impacts

The analyses of air quality impacts require information pertaining to the individual pharmaceutical manufacturing facility, the receiving POTW if indirect dischargers are occurring, the exposed population and long-term average atmospheric conditions in the vicinity of each facility, and the chemicals present in the wastestream. Specific information is obtained from published EPA guidance documents or quality controlled data bases maintained by EPA headquarters program offices, if available. Other data sources include documents or data bases produced or maintained by other Federal agencies, peer reviewed literature, and secondary sources cited in appropriate EPA documents.

3.2.1 Facility-Specific Data

Information pertaining to an individual facility includes annual chemical loads, latitude and longitude coordinates, and side dimensions and elevation of on-site biological treatment units (Appendix E). For the analysis of fugitive emissions from open air biological treatment, two sets of annual chemical loads are examined. The Engineering and Analysis Division (EAD) provided electronic files of the "low estimate" loading data, which is based on CWA Section 308 Questionnaire responses (December 1994). EAD generated the "maximum estimate" loading data based on conservative assumptions using a wastewater treatment model (WATER7) and a mass balance (December 1994). The "maximum estimate" loading data are engineering estimates representing the upper bound for potential air emissions of volatile organic compounds. Latitude and longitude coordinates are obtained from Section 308 Questionnaire responses or from the Toxic Release Inventory (TRI) data base maintained by the Office of Pollution Prevention and Toxics (OPPT). A single side dimension (in meters) of the on-site equalization tank was taken from surface area values provided in the Section 308 Questionnaire responses. The elevation (used as the fugitive emission release height) is assumed to be 3 meters in all cases. OPPT also makes this assumption in performing screening level exposure assessments conducted under Toxic Substances Control Act (TSCA) authority.

For the analysis of toxic vapor partitioning at POTWs, the concentration of chemical constituents in wastewater transferred to each POTW and the POTW influent flow is required. Chemical concentrations are calculated from annual indirect load and effluent flow data provided by EAD (April 1994). Total POTW influent flow is obtained from the 1992 NEEDS Survey.

3.2.2 Population and Climatologic Data

Factors needed to help determine the potential extent and magnitude of exposure from fugitive releases include population and long-term average atmospheric conditions, as well as the assumed characteristics of exposed persons. The spatial population distribution surrounding a given set of latitude and longitude coordinates is available from 1980 U.S. Census data

incorporated in the GEMS mainframe computer modeling system. GEMS also contains information on long-term average wind speed, wind direction frequency, atmospheric stability, and temperature needed to run the ISCLT model. An average adult body weight of 70 kilograms, an average adult inhalation rate of 20 m^3 per day, and an average lifetime of 70 years are used to represent all exposed persons. These values are reported in the *Exposure Factors Handbook* (U.S. EPA, 1989a)

3.2.3 Information Used to Evaluate Human Health Risks and Benefits

Toxicity assessment for the fugitive emission analysis is based on the chemical-specific ambient reference concentration (RfC) for noncarcinogenic effects, and slope factor (SF) for carcinogenic effects (Appendix E). RfCs and SFs are obtained first from IRIS, and secondarily from the 1992 HEAST. The RfC is an estimate of a daily exposure level (adjusted to concentration units by assuming a 70 kilogram body weight and a 20 m^3 per day inhalation rate) for the human population, including sensitive subpopulations, that is likely to be without an appreciable risk of deleterious noncarcinogenic health effects over a lifetime as defined in *Risk Assessment Guidance for Superfund* (U.S. EPA, 1989b). EPA recommends a threshold level assessment approach because several protective mechanisms must be overcome prior to the appearance of an adverse noncarcinogenic effect. EPA assumes that cancer growth can be initiated from a single cellular event, and, therefore, should not be subject to a threshold level assessment approach. The SF is an upper bound estimate of the probability of cancer per unit intake of a chemical over a lifetime (U.S. EPA, 1989b). The Office of Water recommends use of a 10^{-6} (one excess cancer case per 1,000,000 individuals) acceptable cancer probability in its *Technical Support Document for Water Quality-Based Toxics Control* (U.S. EPA, 1991a).

For the POTW toxic vapor partitioning analysis, chemical-specific data include exposure guidelines/standards for occupational exposure and air-water partitioning coefficients (Appendix E). The American Conference of Governmental Industrial Hygienists (ACGIH) threshold limit values (TLVs), derived for 8-hour day 40-hour week exposure, are used in the

hazard screening procedure. TLVs are obtained from the *Threshold Limit Values for Chemical Substances and Physical Agents and Biological Exposure Indices* (U.S. EPA, ACGIH, 1990d). Henry's Law Constant (HLC), the measured or estimated ratio of vapor pressure to solubility, is used as the air-water partition coefficient. Most HLCs are obtained from the *Toxic Chemical Release Inventory Screening Guide* (U.S. EPA, 1989c), the *Superfund Chemical Data Matrix* (U.S. EPA, 1991b), or the quantitative structure activity relationship (QSAR) system maintained by EPA's Environmental Research Laboratory in Duluth, MN.

3.3 Literature Review

Literature abstracts are obtained through the computerized information system DIALOG which provides access to Enviroline, Pollution Abstracts, Aquatic Science Abstracts, and Water Resources Abstracts. Data are also obtained from the 1990/1992 State Water Quality Assessments (305(b)) Reports, the *Pharmaceutical Outreach Questionnaire* (U.S. EPA, 1993b), newspaper articles (Washington Post, Baltimore Evening Sun), and the 1990 State 304(l) short lists.

4. SUMMARY OF RESULTS

4.1 Projected Water Quality Impacts

4.1.1 Comparison of Instream Concentrations with Ambient Water Quality Criteria[6]

The results of this analysis indicate the water quality benefits of controlling discharges from pharmaceutical manufacturing facilities to surface waters and POTWs. The following two sections summarize potential aquatic life and human health impacts on receiving stream water quality and on POTW operations and their receiving streams for AC and BD direct and indirect discharges[7]. All tables referred to in these sections are presented at the end of Section 4. Appendices F, G, and H present the results of the stream modeling for each type of discharge, respectively.

4.1.1.1 *Direct Discharges*

(a) AC Facilities

The effects of direct wastewater discharges on receiving stream water quality are evaluated at **current** and **steam stripping** treatment levels for 14 facilities discharging 43 pollutants to 14 receiving streams (14 rivers) (Table 1).

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[6]In performing this analysis, EPA used guidance documents published by EPA that recommend numeric human health and aquatic life water quality criteria for numerous pollutants. States often consult these guidance documents when adopting water quality criteria as part of their water-quality standards. However, because those State adopted criteria may vary, EPA used the nationwide criteria guidance as the most representative values.

[7]Three pollutants have been removed as candidates for regulation since this analysis was completed (glycol ethers, bis(chloromethyl) ether and dimethylcarbamyl chloride). In addition, pollutant loadings at **steam stripping** treatment levels have been received and modeled since this analysis was initially completed using **distillation** pollutant loadings. Because the projected loads from these two treatment technologies are roughly comparable, the initial analysis was rerun using the **steam stripping** pollutant loads only for those facilities for which aquatic life or human health criteria excursions or POTW inhibition problems were projected at current loadings.

Pollutant loadings for 14 facilities at **current** discharge levels are 5.13 million pounds-per- year (Table 2). These loadings are reduced to 0.24 million pounds-per-year at **distillation** levels; a reduction of 95 percent. Since **steam stripping** is a less effective treatment technology, a lower reduction in pollutant loadings would occur at **steam stripping discharge levels**.

Instream pollutant concentrations are projected to exceed **human health criteria** or toxic effect levels (developed for water and organisms consumption) in 14 percent (2 of the total 14) of the receiving streams at **current** discharge levels (Table 3). A total of 3 pollutants at **current** are projected to exceed instream criteria or toxic effect levels using a target risk of 10^{-6} for carcinogens (Table 4). No excursions of **human health criteria** or toxic effect levels are projected at **steam stripping** discharge levels (Table 3).

Instream pollutant concentrations are projected to exceed **chronic aquatic life criteria** or toxic effect levels in 7 percent (1 of the total 14) of the receiving streams at **current** discharge levels (Table 3). A total of 2 pollutants at **current** are projected to exceed instream criteria or toxic effect levels (Table 4). No excursions of **chronic aquatic life criteria** or toxic effect levels are projected at **steam stripping** discharge levels (Table 3).

Excursions of **human health criteria** or toxic effect levels (developed for organisms consumption only) and of **acute aquatic life criteria** or toxic effect levels are also presented in Table 3. A similar reduction in the number of pollutants exceeding criteria is noted.

(b) BD Facilities

The effects of direct wastewater discharges on receiving stream water quality are evaluated at **current** and **steam stripping** treatment levels for 3 facilities discharging 6 pollutants to 3 receiving streams (3 rivers) (Table 5).

Pollutant loadings for 3 facilities at **current** discharge levels are 15,780 pounds-per-year (Table 6). These loadings are reduced to 620 pounds-per-year at **distillation** levels; a reduction of 96 percent. Since **steam stripping** is a less effective treatment technology, a lower reduction in pollutant loadings would occur at **steam stripping discharge levels**.

No excursions of **human health criteria** or toxic effect levels or of **aquatic life criteria** or toxic effect levels are projected at **current** or **steam stripping** discharge levels (Table 7).

4.1.1.2 *Indirect Discharges*

(a) AC Facilities

The effects of POTW wastewater discharges of 54 pollutants on receiving stream water quality are evaluated at **current** and **steam stripping** discharge levels, for 61 facilities, which discharge to 43 POTWs on 42 receiving streams (35 rivers and 7 estuaries) (Table 8).

Pollutant loadings for 61 facilities at **current** discharge levels are 29.98 million pounds-per-year (Table 2). The loadings are reduced to 3.44 million pounds-per-year after **distillation pretreatment**; a reduction of 88 percent. Since **steam stripping** is a less effective treatment technology, a lower reduction in pollutant loadings would occur after **steam stripping pretreatment**.

Instream pollutant concentrations are projected to exceed **human health criteria** or toxic effect levels (developed for water and organisms consumption) in 10 percent (4 of the total 42) of the receiving streams at **current** discharge levels (Table 9). A total of 4 pollutants at **current** are projected to exceed instream criteria or toxic effect levels using a target risk of 10^{-6} for the carcinogens (Table 10). Instream concentrations of 1 pollutant are projected to exceed **human health** criteria or toxic effect levels in 5 percent (2 of the total 42) of the receiving streams at **steam stripping pretreatment** discharge levels.

Instream pollutant concentrations are not projected to exceed **chronic aquatic life criteria** or toxic effect levels at **current** or **steam stripping pretreatment** discharge levels (Table 9). No excursions of **human health criteria** or toxic effect levels (developed for organisms consumption only) and of **acute aquatic life criteria** or toxic effect levels are projected (Table 9).

In addition, the potential impacts of 65 facilities, which discharge to 46 POTWs, are evaluated in terms of inhibition of POTW operation and contamination of sludge. Fifty-one (51) pollutants are evaluated for potential POTW operation inhibition. No pollutants are evaluated for potential sludge contamination problems since EPA sludge criteria are not available for any of the pollutants of concern. At **current** discharge levels, inhibition problems are projected to occur at 13 percent (6 of the 46) of the POTWs for 7 pollutants (Tables 11 and 12). Inhibition problems are reduced after **steam stripping pretreatment** to 3 pollutants at 11 percent (5 of the 46) of the POTWs.

(b) BD Facilities

The effects of POTW wastewater discharges of 23 pollutants on receiving stream water quality are evaluated at **current** and **steam stripping pretreatment** discharge levels, for 55 facilities, which discharge to 45 POTWs on 45 receiving streams (31 rivers and 14 estuaries) (Table 13).

Pollutant loadings for 55 facilities at **current** discharge levels are 1.58 million pounds-per-year (Table 6). The loadings are reduced to 0.03 million pounds-per-year after **distillation pretreatment**; a reduction of 98 percent. Since **steam stripping** is a less effective treatment technology, a lower reduction in pollutant loadings would occur after **steam stripping pretreatment**.

Instream pollutant concentrations are projected to exceed **human health criteria** or toxic effect levels (developed for water and organisms consumption) in 2 percent (1 of the total 45) of the receiving streams at **current** discharge levels[8] (Table 14). A total of 1 pollutant at **current** is projected to exceed instream criteria or toxic effect levels using a target risk of 10^{-6} for the carcinogens (Table 15). No excurions of **human health criteria** or toxic effect levels are projected at **steam stripping pretreatment** discharge levels (Table 14).

Instream pollutant concentrations are projected to exceed **chronic aquatic life criteria** or toxic effect levels in 2 percent (1 of the total 45) of the receiving streams at **current** discharge levels (Table 14). A total of 1 pollutant at **current** are projected to exceed instream criteria or toxic effect levels (Table 15). No excursions of **chronic aquatic life criteria** or toxic effect levels are projected at **steam stripping pretreatment** discharge levels.

Excursions of **human health criteria** or toxic effect levels (developed for organism consumption only) and of **acute aquatic life criteria** or toxic effect levels are also presented in Table 14.

In addition, the potential impacts of 61 facilities, which discharge to 50 POTWs, are evaluated in terms of inhibition of POTW operation and contamination of sludge. Twenty-three (23) pollutants are evaluated for potential POTW operation inhibition. No sludge criteria are available to evaluate potential sludge contamination problems. No inhibition problems are projected to occur at **current** or **steam stripping pretreatment** discharge levels (Table 16).

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[8]One additional human health excursion for bis(chloromethyl) ether is projected at **current** and **steam stripping pretreatment** discharge levels; however, bis(chloromethyl) ether hydrolyses very rapidly and is not expected to pose a threat to human health.

4.1.2 Estimation of Human Health Risks and Benefits

The results of this analysis indicate the potential benefits to human health by estimating the risks (carcinogenic and systemic effects) associated with current and reduced pollutant levels in fish tissue and drinking water. The following two sections summarize potential human health impacts from the consumption of fish tissue and drinking water derived from water bodies impacted by AC and BD direct and indirect discharges. Appendices I and J present the results of the modeling for each type of discharge, respectively.

4.1.2.1 *Direct Discharges*

The effects of direct wastewater discharges on human health from the consumption of fish tissue and drinking water are evaluated at current and distillation treatment levels[9] for 17 AC/BD facilities discharging 44 pollutants to 17 receiving streams (17 rivers) (Tables 1 and 5).

(a) Fish Tissue

At current discharge levels, 2 streams, receiving the discharge of 4 carcinogens from 2 facilities, have total estimated individual pollutant cancer risks greater than 10^{-6} (Tables 17 and 18). Total estimated risks (greater than 10^{-6}) range from 2.1E-6 to 7.5E-6 for subsistence fishermen. Total risks greater than 10^{-6} are not projected for the general population or sport fishermen. Total excess annual cancer cases are estimated to be 3.8E-5 for subsistence fishermen. No systemic toxicant effects (hazard index greater than 1.0) are projected. At distillation discharge levels, no total estimated individual pollutant cancer risks greater than 10^{-6} or systemic toxicant effects are projected for the general population, sport fishermen or subsistence fishermen (Tables 17 and 18).

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[9]Pollutant loadings at steam stripping treatment levels have been received since this analysis was initially completed. Since no substantial risks are projected at current, the highest wasteload, none are projected for steam stripping.

(b) **Drinking Water**

At current discharge levels, 2 streams, receiving the discharge of 4 carcinogens from 2 facilities, have total estimated individual pollutant cancer risks greater than 10^{-6} (Tables 19 and 20). Estimated risks range from 2.5E-5 to 4.8E-5. However, there is no drinking water utility located within 50 miles downstream of either discharge site. No systemic toxicant effects (hazard index greater than 1.0) are projected (Table 19).

At distillation discharge levels, no streams are projected to have a total estimated individual pollutant cancer risk greater than 10^{-6} (Tables 19 and 20). No systemic toxicant effects (hazard index greater than 1.0) are projected (Table 19).

4.1.2.2 *Indirect Discharges*

The effects of POTW wastewater discharges on human health from the consumption of fish tissue and drinking water are evaluated at current and distillation discharge levels[10] for 116 AC/BD facilities that discharge 55 pollutants to 77 POTWs on 74 receiving streams (59 rivers and 15 estuaries) (Tables 8 and 13).

(a) **Fish Tissue**

At current discharge levels, 1 stream, receiving the discharge from 4 facilities, has a total estimated individual pollutant cancer risk greater than 10^{-6} from 5 carcinogens (Tables 21 and 22). Total estimated risk is 3.8E-6 for subsistence fishermen. Total risks greater than 10^{-6} are not projected for the general population or sport fishermen. Total excess annual cancer

[10]Pollutant loadings at steam stripping pretreatment levels have been received since this analysis was initially completed. Since no substantial risks are projected at current, the highest wasteload, none are projected for steam stripping.

cases are estimated at 2.4E-5 for **subsistence fishermen**. No systemic toxicant effects (hazard index greater than 1.0) are projected (Table 21).

At **distillation pretreatment** discharge levels, no streams are projected to have total estimated individual pollutant cancer risks greater than 10^{-6} (Tables 21 and 22). No systemic toxicant (hazard index greater than 1.0) are projected (Table 21).

(b) Drinking Water

At **current** discharge levels, 6 streams, receiving the discharge of 6 carcinogens from 10 facilities, have total estimated individual pollutant cancer risks greater than 10^{-6} (Tables 23 and 24). Estimated risks range from 1.3E-6 to 1.8E-5. Two (2) streams, receiving the discharge of 3 carcinogens from 2 facilities, have drinking water utilities located within 50 miles downstream. The total estimated individual pollutant cancer risks range from 1.3E-6 to 1.9E-6. The total number of estimated annual excess cancer cases is 2.2E-3. No systemic toxicant effects (hazard index greater than 1.0) are projected (Table 23).

At **distillation pretreatment** discharge levels, 1 stream, receiving the discharge of 2 carcinogens from 1 facility, has a total estimated individual pollutant cancer risk greater than 10^{-6} (Tables 23 and 24). The total estimated individual pollutant cancer risk is 1.5E-7. However, there is no drinking water utility located within 50 miles downstream of discharge site. Thus, annual excess cancer cases cannot be projected. No systemic toxicant effects (hazard index greater than 1.0) are projected (Table 23).

4.2 Projected Air Quality Impacts

The results of this analysis indicate the potential air quality risks and benefits of controlling fugitive air emission discharges from AC direct and AC and BD indirect discharging pharmaceutical manufacturing facilities. Projected occupational exposure benefits are presented for the control of discharges to POTWs. The following two sections summarize potential human

health risks resulting from fugitive emissions of volatile organics originating from pharmaceutical manufacturing wastewater at the "low estimate" and "maximum estimate" loadings. The third section presents occupational exposure benefits of controlling discharges from pharmaceutical manufacturing facilities to POTWs.

4.2.1 Comparison of Human Health Risks and Benefits (Fugitive Air Emissions)

The potential air quality benefits of controlling fugitive air emissions from AC direct and AC and BD indirect discharging pharmaceutical manufacturing facilities are presented below. The "low estimate" and "maximum estimate" loads are presented separately.

The results of the air quality benefits are presented based on modeling a subset of the overall loading data (Appendix K). The subset is defined using a screening method to rank facility-pollutant releases based on the maximum potential downwind concentration and pollutant levels of concern (Appendix K). Facilities with screening hazard ratios above 1.0 are selected for site-specific analysis. The screening procedure significantly reduces the number of facility-pollutant release combinations that are modeled.

4.2.1.1 *"Low Estimate"*

The preliminary screening method evaluates 45 facilities discharging 50 pollutants via fugitive emissions. There are 288 facility-pollutant loads, releasing 7.08 million pounds of pollutants per year. Under the assumptions listed in the methodology section, the benefit associated with the control of fugitive emissions is based on loading values from EPA's 308 questionnaire survey.

The screening procedure identifies 22 facility-pollutant discharges with hazard ratios greater than 1.0. These releases represent 10 pollutants from 14 facilities at a benefit load of approximately 2.5 million pounds-per-year. Atmospheric modeling includes 17 facility-pollutant

releases of 6 carcinogens. Four additional facility-pollutant releases of 4 non-carcinogenic pollutants were analyzed.

Based on the "low estimate" load benefits, 190,220 people nationwide are projected to be exposed to risk levels exceeding 10^{-6} (Table 25). Projected "low estimate" load benefits include 0.023 excess annual cancer occurrences. Chloroform has the largest impact of any single chemical based on the "low estimate" load benefits. The GAMS air modeling analysis did not project any population exposed to ambient levels above the threshold for non-carcinogenic effects.

Three pollutants; bis(chloromethyl) ether, dimethyl carbamyl chloride, and glycol ethers, are not included in the air quality modeling analysis. These pollutants are no longer considered for regulation in the pharmaceutical manufacturing industry.

4.2.1.2 *"Maximum Estimate"*

The preliminary screening method evaluated 84 facilities discharging 52 pollutants via fugitive emissions. There are 453 facility-pollutant loads, generating a maximum potential benefit of 38 million pounds of pollutants reduced per year.

The screening procedure identified 43 facility-pollutant scores with hazard ratios greater than 1.0. These air modeling applications include 23 facilities with a maximum benefit loading of approximately 11.6 million pounds per year for 12 pollutants. These include 27 carcinogenic and 16 systemic releases of 6 carcinogenic and 6 non-carcinogenic pollutants, respectively.

The "maximum estimate" air quality modeling analysis projects 2.4 million people (1990 population) at cancer risk levels exceeding 10^{-6} would benefit from the air load reduction (Table 26). The load reduction would provide a benefit of 0.35 reduced annual cancer case occurrences. Chloroform and methylene chloride cause the greatest potential carcinogenic effects based on the "maximum estimate" loads. In addition, the air modeling analysis projects

that approximately 126 thousand people would benefit from the reduced exposure to chemicals associated with non-carcinogenic effects, principally triethylamine.

Three pollutants (bis(chloromethyl) ether, dimethyl carbomyl chloride, and glycol ethers) are not included in the summary for the "maximum estimate" analysis. These pollutants are not currently included in the proposed regulation.

4.2.2 Comparison of POTW Occupational Risks and Benefits

Pollutant loadings at **current** discharge levels for 129 pharmaceutical manufacturing facilities discharging a total of 32.6 million pounds-per-year to 85 POTWs are analyzed. The loadings are reduced to 3.47 million pounds-per-year at the **full distillation pretreatment**. This represents a 89 percent decrease. Since **steam stripping** is a less effective treatment technology, a lower reduction in pollutant loadings would occur at **steam stripping pretreatment**.

A total of 12 POTWs treating 52 pollutants are identified with summed hazard ratios greater than 1.0 at the **current** discharge levels. Individual pollutant hazard ratios ranged from 2.6E-10 to 2,530 at the **current** discharge levels, with 23 occurrences of 10 pollutants exceeding the hazard ratio of 1.0 at the same POTW (Table 27). Benzene is associated with the greatest risk to POTW workers.

A total of 7 POTWs treating 44 pollutants are identified with summed hazard ratios greater than 1.0 at **full distillation pretreatment** discharge levels. Individual pollutant hazard ratios ranged from 0 to 25.8 with 6 occurrences of 3 pollutants exceeding the hazard ratio of 1.0 (Table 27). At **steam stripping pretreatment** discharge levels, which are slightly higher than **distillation** levels, 6 to 12 POTWs treating 52 pollutants are projected with summed hazard ratios greater than 1.0.

4.3 Documented Environmental Impacts

In a review of literature abstracts, State 305(b) reports, newspaper articles, and the Pharmaceutical Outreach Questionnaire, 16 studies noted environmental impacts from pharmaceutical manufacturing (Table 28). Impacts included: (1) human health problems (worker exposure and population) such as dizziness, nausea, respiratory and dermal problems and endocrine dysfunction (reproductive); (2) aquatic life effects, such as fish kills; (3) effects on the quality of receiving waters, groundwater, soils, sediments, and drinking water; and (4) impairments to POTW operations. In addition, 4 pharmaceutical manufacturing facilities are identified by States as being point sources causing water quality problems and are included on their 304(l) Short List. Section 304(l) of the Water Quality Act of 1987 requires States to identify waterbodies impaired by the presence of toxic substances, to identify point source discharges of these toxics, and to develop Individual Control Strategies (ICSs) for these discharges. The Short List is a list of waters for which a State does not expect applicable water quality standards (numeric or narrative) to be achieved after technology-based requirements have been met due entirely or substantially to point source discharges of Section 307(a) toxics. A list of facilities included on the 304(l) Short List are provided in Table 28.

Table 1. Frequency of Pollutants from 14 AC Direct Pharmaceutical Manufacturing Facilities Discharging to 14 Receiving Streams

Pollutant Name	Number of Detections by Facility
ACETONE	8
ACETONITRILE	3
AMMONIUM HYDROXIDE	6
AMYL ALCOHOL	1
AMYL ACETATE, n-	2
BUTANOL, 1-	1
BUTYL ACETATE, n-	1
CHLOROFORM	4
CHLOROMETHANE	2
CYANIDE	4
CYCLOHEXANE	2
DICHLOROETHANE, 1,2-	3
DIETHYL ETHER	3
DIMETHYL SULFOXIDE	1
DIMETHYLACETAMIDE, N,N	1
DIMETHYLAMINE	1
DIMETHYLFORMAMIDE, N,N	2
ETHANOL	6
ETHYL ACETATE	5
ETHYLENE GLYCOL	2
FORMALDEHYDE	5
FORMAMIDE	1
FURFURAL	2
HEPTANE, n-	1
HEXANE, n-	3
ISOPROPANOL	8
ISOPROPYL ACETATE	1
ISOPROPYL ETHER	2
METHANOL	7
METHYL ETHYL KETONE	2
METHYL FORMATE	2
METHYL ISOBUTYL KETONE	1
METHYLAMINE	1
METHYLENE CHLORIDE	5
METHYLPYRIDINE, 2-	1
PHENOL	1
PROPANOL, 1-	1
PYRIDINE	1
TERT-BUTYL ALCOHOL	1
TETRAHYDROFURAN	3
TOLUENE	6
TRIETHYLAMINE	1
XYLENES	4

Note: Only pollutants proposed for regulation are evaluated. (Three pollutants have been removed as candidates for regulation since this analysis was completed - glycol ethers, bis(chloromethyl) ether and dimethylcarbamyl chloride).

Source: Engineering and Analysis Division (EAD), March 1994.

Table 2. Summary of Pollutant Loadings for AC Direct and Indirect Pharmaceutical Manufacturers*

	Loadings, pounds-per-year		
	Direct	Indirect	Total
Current			
Organics	4,314,840	29,452,484	33,767,324
Cyanide	45	1,083	1,128
Ammonium Hydroxide	817,732	526,370	1,344,102
Total	**5,132,617**	29,979,937	35,112,554
Distillation* **			
Organics	167,320	3,349,795	3,517,115
Cyanide	6	62	68
Ammonium Hydroxide	71,167	88,514	159,681
Total	**238,493**	3,438,371	3,676,864
No. of Pollutants	43	54	**58
No. of Facilities (Evaluated)	14	61	75

* Only pollutants proposed for regulation are evaluated. (Three Pollutants have been removed as candidates for regulation since this analysis was completed - glycol ethers, bis(chloromethyl) ether and dimethylcarbamyl chloride).

** The same pollutant may be discharged from a number of facilities; therefore, the total does not equal the sum of pollutants.

*** Analysis not conducted for **steam stripping**.

Table 3. Summary of Projected Criteria Excursions for AC Direct Pharmaceutical Dischargers

	Acute Aquatic Life	Chronic Aquatic Life	Human Health Water and Orgs.	Human Health Orgs. Only	Total*
Current					
Stream (No.)	1	1	2	0	3
Pollutants (No.)	2 (3.6)	2 (30.2)	3 (16.0 - 32.0)	0	5
Total Excursions	**2**	**2**	**3**	**0**	
Steam Stripping					
Stream (No.)	0	0	0	0	0
Pollutants (No.)	0	0	0	0	0
Total Excursions	**0**	**0**	**0**	**0**	

NOTE: Number in parentheses represents magnitude of excursions.
Number of streams evaluated = 14 and number of pollutants evaluated = 43.
Only pollutants proposed for regulation are evaluated (Three pollutants have been removed as candidates for regulation since this analysis was completed - glycol ethers, bis(chloromethyl) ether and dimethylcarbamyl chloride).

* Pollutants may exceed criteria on a number of streams; therefore, total does not equal sum of pollutants exceeding criteria.

Table 4. Summary of Pollutants Projected to Exceed Criteria for AC Direct Pharmaceutical Dischargers

		Number of Excursions			
	Number of Detections	Acute Aquatic Life	Chronic Aquatic Life	Human Health Water and Orgs.	Human Health Orgs. Only
Ammonium Hydroxide	6	1 (0)	1 (0)	0	0
Chloromethane	2	0	0	1 (0)	0
Dichloroethane, 1,2-	3	0	0	1 (0)	0
Isopropanol	8	1 (0)	1 (0)	0	0
Methylene Chloride	5	0	0	1 (0)	0
Total	24	2 (0)	2 (0)	3 (0)	0

NOTE: Number of pollutants evaluated = 43.
Numbers represent excursions at **current** treatment levels; numbers in parentheses represent excursions at **steam stripping** treatment levels.
Only pollutants proposed for regulation are evaluated. (Three pollutants have been removed as candidates for regulation since this analysis was completed - glycol ethers, bis(chloromethyl) ether and dimethylcarbamyl chloride).

Table 5. Frequency of Pollutants from 3 BD Direct Pharmaceutical Manufacturing Facilities Discharging to 3 Receiving Streams

Pollutant Name	Number of Detections by Facility
ACETONE	1
ETHANOL	2
FORMALDEHYDE	1
ISOPROPANOL	2
METHANOL	1
POLYETHYLENE GLYCOL 600	1

Note: Only pollutants proposed for regulation are evaluated. (Three pollutants have been removed as candidates for regulation since this analysis was completed - glycol ethers, bis(chloromethyl) ether and dimethylcarbamyl chloride).

Source: Engineering and Analysis Division (EAD), March 1994.

Table 6. Summary of Pollutant Loadings for BD Direct and Indirect Pharmaceutical Manufacturers*

	Loadings, pounds-per-year		
	Direct	Indirect	Total
Current			
Organics	15,780	1,576,114	1,591,894
Cyanide	0	0	0
Ammonium Hydroxide	0	146	146
TOTAL	**15,780**	**1,576,260**	**1,592,040**
Distillation* **			
Organics	620	30,348	30,968
Cyanide	0	0	0
Ammonium Hydroxide	0	25	25
TOTAL	**620**	**30,373**	**30,993**
No. of Pollutants	6	23	**23
No. of Facilities (Evaluated)	3	55	58

* Only pollutants proposed for regulation are evaluated. (Three pollutants have been removed as candidates for regulation since this analysis was completed - glycol ethers, bis(chloromethyl) ether and dimethylcarbamyl chloride).

** The same pollutant may be discharged from a number of facilities; therefore, the total does not equal the sum of pollutants.

*** Analysis not conducted for **steam stripping**.

Table 7. Summary of Projected Criteria Excursions for BD Direct Pharmaceutical Dischargers

	Acute Aquatic Life	Chronic Aquatic Life	Human Health Water and Orgs.	Human Health Orgs. Only	Total
Current					
Stream (No.)	0	0	0	0	0
Pollutants (No.)	0	0	0	0	0
Total Excursions	**0**	**0**	**0**	**0**	
Steam Stripping					
Stream (No.)	0	0	0	0	0
Pollutants (No.)	0	0	0	0	0
Total Excursions	**0**	**0**	**0**	**0**	

NOTE: Number of streams evaluated = 3 and number of pollutants evaluated = 6.
Only pollutants proposed for regulation are evaluated. (Three pollutants have been removed as candidates for regulation since this analysis was completed - glycol ethers, bis(chloromethyl) ether and dimethylcarbamyl chloride).

Table 8. Frequency of Pollutants from 61 AC Indirect Pharmaceutical Manufacturing Facilities Which Discharge to 43 POTWS on 42 Receiving Streams

Pollutant Name	Number of Detections by Facility
ACETONE	30
ACETONITRILE	10
AMMONIUM HYDROXIDE	19
AMYL ALCOHOL	5
AMYL ACETATE, n-	2
ANILINE	4
BENZENE	1
BUTANOL, 1-	14
BUTYL ACETATE, n-	2
CHLOROBENZENE	4
CHLOROFORM	7
CHLOROMETHANE	1
CYANIDE	4
CYCLOHEXANE	2
DICHLOROBENZENE, 1,2-	2
DICHLOROETHANE, 1,2-	3
DIETHYL ETHER	3
DIETHYLAMINE	7
DIMETHYL SULFOXIDE	10
DIMETHYTLACETAMIDE, N,N	6
DIMETHYLANILINE, N,N-	1
DIMETHYLCARBAMYL CHLORIDE	1
DIMETHYLFORMAMIDE, N,N	19
DIOXANE, 1,4-	5
ETHANOL	38
ETHYL ACETATE	17
ETHYLENE GLYCOL	7
ETHYLENE GLYCOL MONOETHYL ETHER	3
FORMALDEHYDE	9
FORMAMIDE	3
HEPTANE, n-	10
HEXANE, n-	4
ISOBUTYRALDEHYDE	2
ISOPROPANOL	39
ISOPROPYL ACETATE	7
ISOPROPYL ETHER	2
METHANOL	43
METHYL CELLOSOLVE	4
METHYL ETHYL KETONE	3
METHYL FORMATE	1
METHYL ISOBUTYL KETONE	6
METHYLAMINE	2
METHYLENE CHLORIDE	26
PETROLEUM NAPTHA	2
PHENOL	6
POLYETHYLENE GLYCOL 600	5
PROPANOL,1-	4
PYRIDINE	7
TERT-BUTYL ALCOHOL	4
TETRAHYDROFURAN	13
TOLUENE	31
TRICHLOROFLUOROMETHANE	1
TRIETHYLAMINE	10
XYLENES	10

Note: Only pollutants proposed for regulation are evaluated. (Three pollutants have been removed as candidates for regulation since this analysis was completed - glycol ethers, bis(chloromethyl) ether and dimethylcarbamyl chloride).
Source: Engineering and Analysis Division (EAD), March 1994.

Table 9. Summary of Projected Criteria Excursions for AC Indirect Pharmaceutical Dischargers

	Acute Aquatic Life	Chronic Aquatic Life	Human Health Water and Orgs.	Human Health Orgs. Only	Total*
Current					
Stream (No.)	0	0	4	0	4
Pollutants (No.)	0	0	4 (1.5 - 9.3)	0	4
Total Excursions	**0**	**0**	**6**	**0**	
Steam Stripping					
Stream (No.)	0	0	2	0	0
Pollutants (No.)	0	0	1 (1.2 - 2.3)	0	0
Total Excursions	**0**	**0**	**0**	**0**	

NOTE: Number in parentheses represents magnitude of excursions.
Number of streams evaluated = 42 and number of pollutants evaluated = 54.
Only pollutants proposed for regulation are evaluated. (Three pollutants have been removed as candidates for regulation since this analysis was completed - glycol ethers, bis(chloromethyl) ether and dimethylcarbamyl chloride).

* Pollutants may exceed criteria on a number of streams; therefore, total does not equal sum of pollutants exceeding criteria.

Table 10. Summary of Pollutants Projected to Exceed Criteria for AC Indirect Pharmaceutical Dischargers

		Number of Excursions			
	Number of Detections	Acute Aquatic Life	Chronic Aquatic Life	Human Health Water and Orgs.	Human Health Orgs. Only
BENZENE	1	0	0	1 (0)	0
CHLOROFORM	7	0	0	1 (0)	0
DICHLOROETHANE, 1,2-	3	0	0	2 (2)	0
METHYLENE CHLORIDE	26	0	0	2 (0)	0
TOTAL	37	0	0	6 (2)	0

NOTE: Number of pollutants evaluated = 54.
Numbers represent excursions at current treatment levels; numbers in parentheses represent excursions at steam stripping pretreatment levels.
Only pollutants proposed for regulation are evaluated. (Three pollutants have been removed as candidates for regulation since this analysis was completed - glycol ethers, bis(chloromethyl) ether and dimethylcarbamyl chloride).

Table 11. Summary of Projected POTW Inhibition and Sludge Contamination Problems from AC Indirect Pharmaceutical Dischargers

	Biological Inhibition	Sludge Contamination*	Total
Current			
POTWs (No.)	6		6
Pollutants (No.)	7		7
Total Problems	**10**		
Steam Stripping			
POTWs (No.)	5		5
Pollutants (No.)	3		3
Total Problems	**6**		

NOTE: Number of POTWs evaluated = 46.
Only pollutants proposed for regulation are evaluated. (Three pollutants have been removed as candidates for regulation since this analysis was completed - glycol ethers, bis(chloromethyl) ether and dimethylcarbamyl chloride).

* No sludge criteria were available for pollutants evaluated.

Table 12. Summary of Pollutants From AC Indirect Pharmaceutical Dischargers Projected to Cause POTW Inhibition and Sludge Contamination Problems

		Number of Excursions	
	Number of Detections	Biological Inhibition	Sludge Contamination*
ACETONITRILE	10	3 (3)	
DIETHYLAMINE	7	1 (0)	
DIMETHYLACETAMIDE, N,N-	6	2 (2)	
DIMETHYL FORMAMIDE, N,N-	19	1 (1)	
FORMAMIDE	3	1 (0)	
PYRIDINE	7	1 (0)	
TRIETHYLAMINE	10	1 (0)	
TOTAL	**62**	**10 (6)**	

NOTE: Numbers represent excursions at **current** treatment levels; numbers in parentheses represent excursions after **steam stripping pretreatment** levels.
Only pollutants proposed for regulation are evaluated. (Three pollutants have been removed as candidates for regulation since this analysis was completed - glycol ethers, bis(chloromethyl) ether and dimethylcarbamyl chloride).

* No sludge criteria were available for pollutants evaluated.

Table 13. Frequency of Pollutants from 55 BD Indirect Pharmaceutical Manufacturing Facilities Which Discharge to 45 POTWS on 45 Receiving Streams

Pollutant Name	Number of Detections by Facility
ACETONE	4
AMMONIUM HYDROXIDE	4
AMYL ACETATE, n-	1
BIS(CHLOROMETHYL)ETHER	1
BUTANOL, 1-	2
CHLOROFORM	1
DIETHYL ETHER	2
DIMETHYL SULFOXIDE	3
ETHANOL	32
ETHYL ACETATE	2
ETHYLENE GLYCOL	3
ETHYLENE GLYCOL MONOETHYL ETHER	3
FORMALDEHYDE	6
HEXANE, n-	1
ISOPROPANOL	22
ISOPROPYL ACETATE	1
ISOPROPYL ETHER	1
METHANOL	16
METHYLENE CHLORIDE	9
PHENOL	7
POLYETHYLENE GLYCOL 600	4
PYRIDINE	1
TOLUENE	1

Note: Only pollutants proposed for regulation are evaluated. (Three pollutants have been removed as candidates for regulation since this analysis was completed - glycol ethers, bis(chloromethyl) ether and dimethylcarbamyl chloride).

Source: Engineering and Analysis Division (EAD), April 1994.

Table 14. Summary of Projected Criteria Excursions for BD Indirect Pharmaceutical Dischargers

	Acute Aquatic Life	Chronic Aquatic Life	Human Health Water and Orgs.	Human Health Orgs. Only	Total*
Current					
Stream (No.)	0	1	2**	1**	2
Pollutants (No.)	0	1 (1.3)	2 (1.3-72E4)**	1 (1467)**	3
Total Excursions	**0**	**1**	**2****	**1****	
Steam Stripping					
Stream (No.)	0	0	1**	1**	1
Pollutants (No.)	0	0	1 (11E3)**	1 (21.6)**	1
Total Excursions	**0**	**0**	**1****	**1****	

NOTE: Number in parentheses represents magnitude of excursions.
Number of streams evaluated = 45 and number of pollutants evaluated = 23.
Only pollutants proposed for regulation are evaluated. (Three pollutants have been removed as candidates for regulation since this analysis was completed - glycol ethers, bis(chloromethyl) ether and dimethylcarbamyl chloride).

* Pollutants may exceed criteria on a number of streams; therefore, total does not equal sum of pollutants exceeding criteria.

** One human health excursion for bis(chloromethyl) ether is projected; however, bis(chloromethyl) ether hydrolyses very rapidly and is not expected to pose a threat to human health.

Table 15. Summary of Pollutants Projected to Exceed Criteria for BD Indirect Pharmaceutical Dischargers

		Number of Excursions			
	Number of Detections	Acute Aquatic Life	Chronic Aquatic Life	Human Health Water and Orgs.	Human Health Orgs. Only
BIS(CHLOROMETHYL)ETHER	1	0	0	1 (1)*	1 (1)
ETHANOL	32	0	1 (0)	0	0
METHYLENE CHLORIDE	9	0	0	1 (0)	0
TOTAL	**42**	**0**	**1 (0)**	**2 (1)**	**1 (1)**

NOTE: Number of pollutants evaluated = 23.
Numbers represent excursions at **current** treatment levels; numbers in parentheses represent excursions at **steam stripping pretreatment** levels.
Only pollutants proposed for regulation are evaluated. (Three pollutants have been removed as candidates for regulation since this analysis was completed - glycol ethers, bis(chloromethyl) ether and dimethylcarbamyl chloride).

* One human health excursion for bis(chloromethyl) ether is projected; however, bis(chloromethyl) ether hydrolyses very rapidly and is not expected to pose a threat to human health.

Table 16. Summary of Projected POTW Inhibition and Sludge Contamination Problems from BD Indirect Pharmaceutical Dischargers

	Biological Inhibition	Sludge Contamination*	Total*
Current			
POTWs (No.)	0		0
Pollutants (No.)	0		0
Total Problems	0		
Steam Stripping			
POTWs (No.)	0		0
Pollutants (No.)	0		0
Total Problems	0		

NOTE: Number of POTWs evaluated = 50.
Only pollutants proposed for regulation are evaluated. (Three pollutants have been removed as candidates for regulation since this analysis was completed - glycol ethers, bis(chloromethyl) ether and dimethylcarbamyl chloride).

* No sludge criteria were available for pollutants evaluated.

Table 17. Summary of Potential Human Health Impacts for AC/BD Direct Pharmaceutical Dischargers (Fish Tissue Consumption)

	Total Individual Cancer Risks > 10^{-6}	Total Excess Annual Cancer Cases	Hazard Indices > 1.0
Current			
Stream (No.)/Facilities (No.)	2/2	NA/NA	0/0
Carcinogens (No.)	4	NA	0
General Population	0	NA	0
Sport Fishermen	0	NA	0
Subsistence Fishermen	2 (2.1E-6 to 7.5E-6)	3.8E-5	0
TOTAL		**3.8E-5**	
Distillation*			
Stream (No.)/Facilities (No.)	0/0	NA/NA	0/0
Carcinogens (No.)	0	NA	0
General Population	0	NA	0
Sport Fishermen	0	NA	0
Subsistence Fishermen	0	NA	0

NOTE: Total number of streams evaluated = 17 and total number of pollutants = 44.
Only pollutants proposed for regulation are evaluated. (Three pollutants have been removed as candidates for regulation since this analysis was completed - glycol ethers, bis(chloromethyl)ether, and dimethylcarbamyl chloride).
NA = Not Applicable.

* Analysis was not conducted for steam stripping.

Table 18. Summary of Pollutants Projected to Cause Human Health Impacts for AC/BD Direct Pharmaeutical Dischargers at Current Discharge Levels*
(Fish Tissue Consumption)

	Cancer Risks > 10^{-6}/ Excess Annual Cancer Cases General Population	Cancer Risks > 10^{-6}/ Excess Annual Cancer Cases Sport Fishermen	Cancer Risks > 10^{-6}/ Excess Annual Cancer Cases Subsistence Fishermen
Stream No. 1			
Methylene Chloride	0/NA	0/NA	1.0E-6/3.4E-6
Chloroform	0/NA	0/NA	2.6E-8/8.7E-8
Chloromethane	0/NA	0/NA	6.5E-6/2.2E-5
TOTAL			**7.5E-6/2.5E-5**
Stream No. 2			
Chloroform	0/NA	0/NA	3.7E-9/2.3E-8
Dichloroethane, 1,2-	0/NA	0/NA	2.1E-6/1.3E-5
TOTAL			**2.1E-6/1.3E-5**

NOTE: Total number of streams evaluated = 17 and total number of pollutants = 44.
Only pollutants proposed for regulation are evaluated. (Three pollutants have been removed as candidates for regulation since this analysis was completed - glycol ethers, bis(chloromethyl)ether, and dimethylcarbamyl chloride).
NA = Not Applicable

* No total cancer risks greater than 10^{-6} are projected at **distillation** discharge levels.

Table 19. Summary of Potential Human Health Impacts for AC/BD Direct Pharmaceutical Dischargers (Drinking Water Consumption)

	Total Individual Cancer Risks > 10^{-6}	Total Excess Annual Cancer Cases	Hazard Indices > 1.0
Current			
Stream (No.)	2 (2.5E-5 to 4.8E-5)	NA	0
Carcinogens (No.)	4	NA	0
With Drinking Water Utility ≤ 50 miles	0	NA	0
Carcinogens (No.)	0	NA	0
Distillation*			
Stream (No.)	0	NA	0
Carcinogens (No.)	0	NA	0
With Drinking Water Utility ≤ 50 miles	0	NA	0
Carcinogens (No.)	0	NA	0

NOTE: Total number of streams evaluated = 17 and total number of pollutants = 44.
Only pollutants proposed for regulation are evaluated. (Three pollutants have been removed as candidates for regulation since this analysis was completed - glycol ethers, bis(chloromethyl)ether, and dimethylcarbamyl chloride).
NA = Not Applicable

* Analysis was not completed for **steam stripping**.

Table 20. Summary of Pollutants Projected to Cause Human Health Impacts for AC/BD Direct Dischargers (Drinking Water Consumption)

	Current Discharge Levels Cancer Risks > 10^{-6}/ Excess Annual Cancer Cases	Distillation Discharge Levels** Cancer Risks > 10^{-6}/ Excess Annual Cancer Cases
Stream No. 1*		
Methylene Chloride	1.6E-5/NA	0/NA
Chloroform	9.9E-8/NA	0/NA
Chloromethane	3.2E-5/NA	0/NA
TOTAL	**4.8E-5/NA**	
Stream No. 2*		
Chloroform	1.4E-8/NA	0/NA
Dichloroethane, 1,2-	2.5E-5/NA	0/NA
TOTAL	**2.5E-5/NA**	

NOTE: Total number of streams evaluated = 17 and total number of pollutants = 44.
Only pollutants proposed for regulation are evaluated. (Three pollutants have been removed as candidates for regulation since this analysis was completed - glycol ethers, bis(chloromethyl)ether, and dimethylcarbamyl chloride).
NA = Not Applicable

* No drinking water utility located within 50 miles downstream of discharge site.

** Analysis was not completed for steam stripping.

Table 21. Summary of Potential Human Health Impacts for AC/BD Indirect Pharmaceutical Dischargers (Fish Tissue Consumption)

	Total Individual Cancer Risks $> 10^{-6}$	Total Excess Annual Cancer Cases	Hazard Indices > 1.0
Current			
Stream (No.)/Facilities (No.)	1/4	NA/NA	0/0
Carcinogens (No.)	5	NA	0
General Population	0	NA	0
Sport Fishermen	0	NA	0
Subsistence Fishermen	1 (3.8E-6)	2.4E-5	0
TOTAL		**2.4E-5**	
Distillation*			
Stream (No.)/Facilities (No.)	0/0	NA/NA	0/0
Carcinogens (No.)	0	NA	0
General Population	0	NA	0
Sport Fishermen	0	NA	0
Subsistence	0	NA	0

NOTE: Total number of streams evaluated = 74 and total number of pollutants = 55.
Only pollutants proposed for regulation are evaluated. (Three pollutants have been removed as candidates for regulation since this analysis was completed - glycol ethers, bis(chloromethyl)ether, and dimethylcarbamyl chloride).
NA = Not Applicable.

* Analysis was not completed for **steam stripping**.

Table 22. Summary of Pollutants Projected to Cause Human Health Impacts for AC/BD Indirect Pharmaceutical Dischargers (Fish Tissue Consumption)

	Cancer Risks $> 10^{-6}$/ Excess Annual Cancer Cases General Population	Cancer Risks $> 10^{-6}$/ Excess Annual Cancer Cases Sport Fishermen	Cancer Risks $> 10^{-6}$/ Excess Annual Cancer Cases Subsistence Fishermen
Current Discharge Levels:			
Stream No. 1			
Bis(chloromethyl)ether*	1.5E-3/8.7E-1	3.8E-3/7.7E-1	3.2E-2/3.4E-1
TOTAL	**1.5E-3/8.7E-1**	**3.8E-3/7.7E-1**	**3.2E-2/3.4E-1**
Stream No. 2			
Methylene Chloride	0/NA	0/NA	4.3E-7/2.7E-6
Aniline	0/NA	0/NA	1.5E-7/9.8E-7
Benzene	0/NA	0/NA	3.0E-6/1.9E-5
Dichloroethane, 1,2-	0/NA	0/NA	1.9E-7/1.2E-6
Dioxane, 1,4-	0/NA	0/NA	2.5E-8/1.6E-7
TOTAL			**3.8E-6/2.4E-5**
Distillation Discharge Levels:**			
Stream No. 1			
Bis(chloromethyl) ether*	2.2E-5/1.3E-2	5.5E-5/1.1E-2	4.7E-4/5.0E-3
TOTAL	**2.2E-5/1.3E-2**	**5.5E-5/1.1E-2**	**4.7E-4/5.0E-3**

NOTE: Total number of streams evaluated = 74 and total number of pollutants = 55.
Only pollutants proposed for regulation are evaluated. (Three pollutants have been removed as candidates for regulation since this analysis was completed - glycol ethers, bis(chloromethyl)ether, and dimethylcarbamyl chloride).
NA = Not Applicable

* Bis(chloromethyl) ether hydrolyses very rapidly and is not expected to pose a threat to human health from fish tissue consumption.

** Analysis not completed for **steam stripping**.

Table 23. Summary of Potential Human Health Impacts for AC/BD Indirect Pharmaceutical Dischargers (Drinking Water Consumption)

	Total Individual Cancer Risks > 10^{-6}	Total Excess Annual Cancer Cases	Hazard Indices > 1.0
Current			
Stream (No.)	6 (1.3E-6 to 1.8E-5)	NA	0
Carcinogens (No.)	6	NA	0
With Drinking Water Utility ≤ 50 miles	2 (1.3E-6 to 1.9E-6)	2.2E-3	0
Carcinogens (No.)	3	NA	0
TOTAL		**2.2E-3**	
Distillation*			
Stream (No.)	1 (1.5E-7)	NA	0
Carcinogens (No.)	2	NA	0
With Drinking Water Utility ≤ 50 miles	0	NA	0
Carcinogens (No.)	0	NA	0

NOTE: Total number of streams evaluated = 74 and total number of pollutants = 55.
Only pollutants proposed for regulation are evaluated. (Three pollutants have been removed as candidates for regulation since this analysis was completed - glycol ethers, bis(chloromethyl)ether, and dimethylcarbamyl chloride).
NA = Not Applicable

* Analysis not completed for **steam stripping**.

Table 24. Summary of Pollutants Projected to Cause Human Health Impacts for AC/BD Indirect Pharmaceutical Discharges (Drinking Water Consumption)

	Current Discharge Levels Cancer Risks $>10^{-6}$/ Excess Annual Cancer Cases	Distillation Discharge Levels*** Cancer Risks $>10^{-6}$/ Excess Annual Cancer Cases
Stream No. 1*		
Methylene Chloride	4.2E-7/3.2E-4	0/NA
Aniline	1.6E-11/1.3E-8	0/NA
Chloroform	1.5E-6/1.2E-3	0/NA
TOTAL	**1.9E-6/1.5E-3**	
Stream No. 2		
Methylene Chloride	4.6E-7/NA	9.4E-10/NA
Dichloroethane, 1,2	1.9E-6/NA	1.5E-7/NA
TOTAL	**2.4E-6/NA**	**1.5E-7/NA**
Stream No. 3		
Methylene Chloride	2.0E-6/NA	0/NA
Chloroform	1.0E-7/NA	0/NA
Dioxane, 1,4-	1.7E-7/NA	0/NA
TOTAL	**2.3E-6/NA**	
Stream No. 4*		
Methylene Chloride	1.3E-6/7.5E-4	0/NA
TOTAL	**1.3E-6/7.5E-4**	
Stream No. 5		
Bis(chloromethyl)ether**	7.2E-1/NA	1.1E-2/NA
TOTAL	**7.2E-1/NA**	**1.1E-2/NA**
Stream No. 6		
Methylene Chloride	6.8E-6/NA	0/NA
Aniline	1.1E-7/NA	0/NA
Benzene	8.2E-6/NA	0/NA
Dichloroethane, 1,2-	2.3E-6/NA	0/NA
Dioxane, 1,4-	9.1E-7/NA	0/NA
TOTAL	**1.8E-5/NA**	

NOTE: Total number of streams evaluated = 74 and total number of pollutants = 55.
Only pollutants proposed for regulation are evaluated. (Three pollutants have been removed as candidates for regulation since this analysis was completed - glycol ethers, bis(chloromethyl)ether, and dimethylcarbamyl chloride).
NA = Not Applicable

* Drinking water utility located within 50 miles downstream of discharge site.

** Bis(chloromethyl)ether hydrolyses very rapidly and is not expected to pose a threat to human health from drinking water consumption.

*** Analysis not completed for steam stripping.

Table 25. Summary of Air Quality Modeling Analysis for Pharmaceutical Fugitive Emissions
(Low End Estimate Loading)

Pollutant Name	Population Benefit	Excess Lifetime Cancer Case Benefit	Excess Annual Cancer Case Benefit	Population Benefit (Systemic)	Number of Occurrences
Benzene	723	3.18E-02	4.54E-04		1
Chloroform	154,965	1.32E+00	1.89E-02		5
Chloromethane	0	3.50E-04	5.00E-06		1
Dichloroethane, 1,2-	4,878	9.47E-02	1.35E-03		1
Dimethylformamide,N,N-				0	1
Formaldehyde	0	2.16E-03	3.09E-05		1
Methyl cellosolve				0	1
Methylene chloride	32,358	1.57E-01	2.25E-03		9
Toluene				0	1
Triethylamine				0	1
TOTAL	**190,220**	**1.6**	**0.023**	**0**	**22**

NOTE: To avoid double-counting, the largest facility - pollutant benefit population was used at each site in the total benefit population calculation.

Table 26. Summary of Air Quality Modeling Analysis for Pharmaceutical Fugitive Emissions
(Maximum Estimate Loading)

Pollutant Name	Population Benefit	Excess Lifetime Cancer Case Benefit	Excess Annual Cancer Case Benefit	Population Benefit (Systemic)	Number of Occurrences
Aniline				0	1
Benzene	0	4.63E-04	6.62E-06		1
Chloroform	130,240	1.22E-00	1.74E-02		7
Chloromethane	0	2.21E-03	3.16E-05		2
Dichloroethane, 1,2-	13,634	2.05E-01	2.93E-03		2
Dimethylformamide, N,N-				0	1
Formaldehyde	1,352	1.54E-02	2.20E-04		3
Hexane, n-				0	3
Methyl cellosolve				29,926	2
Methylene chloride	2,293,347	2.28E+01	3.26E-01		12
Toluene				0	3
Triethylamine				96,824	6
TOTAL	**2,430,991**	**24.27**	**0.35**	**125,533**	**43**

NOTE: To avoid double-counting, the largest facility - pollutant benefit population was used at each site in the total benefit population calculation.

Table 27. Summary of Potential POTW Occupational Exposure Impacts for Pharmaceutical Indirect Discharges

	Total Number	Hazard Score Range
Current		
POTW	85	
w/ Hazard Ratio > 1	12	1.5-2,561
Pollutants	52	
w/Hazard Ratio > 1	10	1.1-2,530
Acetonitrile	4	1.2-25.8
Benzene	1	2,530
Chloroform	2	6.0-16.1
Diethylamine	1	5.0
Dimethylamine	1	9.3
Heptane, n-	5	1.1-6.0
Hexane, n-	2	3.0-62.9
Methylene Chloride	2	3.4-6.7
Toluene	4	1.1-2.2
Triethylamine	1	1.9
Distillation*		
POTW	85	
w/Hazard Ratio > 1	7	1.2-31.1
Pollutants	44	
w/ Hazard Ratio > 1	3	1.1-25.8
Acetonitrile	4	1.2-25.8
Benzene	1	5.3
Hexane, n-	1	1.1

* Analysis not completed for **steam stripping**.

Table 28. Environmental Impact Case Studies of Pharmaceutical Manufacturing Wastes

SITE	FACILITY	EXPOSURE		IMPACTS
		ENVIRONMENT	BIOTA/EFFECT	
Passaic Valley Sewerage Commissioners Newark, New Jersey	POTW	Priority organic pollutants in receiving wastewaters from pharmaceutical facilities.	--	Organics may have passed through system since these pollutants are not analyzed in POTW effluent.
Bergen County Utilities Authority Little Ferry, New Jersey	POTW	High concentration of VOCs in receiving wastewaters from pharmaceutical facilities.	Worker exposure (sewer) to VOCs.	POTW had violations of local limits by pharmaceutical sources for cyanide, oil and grease and total kjeldahl nitrogen. In addition, high concentrations of VOCs found in wastewater discharges.
North Shore Sanitary District Gurnee, Illinois	POTW	High concentration of priority pollutants such as chloroform, methylene chloride, toluene, as well as non-priority pollutants such as tetrahydrofuran, thiobismethane, trimethyl silanol, hydrogen sulfide, and dimethyl disulfide in receiving wastewater from pharmaceutical facility.	POTW operation interference due to tetrahydrofuran.	Violations of local units caused by ammonia. Pass-through of tetrahydrofuran and trimethyl silanol.
Greenville Utilities Commission Greenville, South Carolina	POTW	High concentrations of toluene, acetone, chloroform, methylene chloride, acrylonitrile, ethylene glycol, pyridine, methanol, dimethyl sulfoxide, ethyl alcohol, isopropyl alcohol, acetonitrile and benzene in receiving wastewater from pharmaceutical facility.	POTW operation interference due to dimethyl sulfoxide.	Dimethyl sulfoxide may be inhibiting the nitrification process in biological treatment system. POTW also has total kjeldahl nitrogen violations.
East Hanover TWP New Jersey	Sandoz Pharmaceuticals		--	Impact on surface water quality (details not given).
Kalamazoo, Michigan Portage Creek	Pharmaceutical Plant	Toluene in receiving water.	Toxic effects on fish.	Impacts due to toluene spill from a pharmaceutical plant resulted in 100% kill of brown trout and 50% kill of other species in 1991.
Puerto Rico Aqueduct and Sewer Authority Barceloneta, Puerto Rico	Pharmaceutical Plant			Various odor problems (details not given)

Table 28. Environmental Impact Case Studies of Pharmaceutical Manufacturing Wastes (continued)

SITE	FACILITY	EXPOSURE		IMPACTS
		ENVIRONMENT	BIOTA/EFFECT	
Syracuse, New York Lake Onondaga	Bristol-Myers Squibb Company	Toxics discharged into groundwater and sewer system.	POTW worker exposure to hydrogen sulfide POTW operation interferences due to siloxanes	Since 1986 plant improperly discharging wastes to groundwater (leaks) and discharging excessive levels to POTW. Overload of POTW resulted in pollution of Lake Onondaga. The company agreed to pay a fine of $3.5 million and to build a waste-water treatment plant for the NY facility by 1996 at an estimated cost of $30 million. Odor control study and volatile compounds study currently underway by POTW.
Boulder, Colorado	Pharmaceutical Manufacturing/ R&D plant	VOCs in groundwater (on and off-site).	--	Plant records confirmed that on-site groundwater contamination resulted from historical and accidental spills of organic compounds.
Harriman, New York Ramapo River	Nepera Chemical	Ammonia discharged into sewer system.	Toxic effects on fish due to low oxygen levels.	Impacts on the Ramapo River due to discharges from Orange County Sewer District No. 1 POTW. Fish kill also occurred. Nepera Chemical was subject of an enforcement hearing concerning alleged violations of its discharge permit limitations for ammonia. Problem has been resolved.
Springfield, Missouri	Syntex	Dichloroethylene, methylene chloride, benzene and toluene in groundwater.	--	Not yet detected in water supply wells.
Guayama, Puerto Rico	Pharmaceutical Manufacturing Plant and Former Synthetic Fiber Manufacturing Plant	Toxics in soil and groundwater (public supply wells). Presence of acetone, methyl ethyl ketone, methylene chloride and bis(2-ethyl hexyl) phthalate in soil. Perchloroethylene, trichloroethylene, vinyl chloride, and trichlorofluoromethane in the supply wells.	Population and worker exposure.	Direct contact with and ingestion of contaminated soil by workers and area residents who access the site. Impacts can also occur from ingestion and direct contact with groundwater.

Table 28. Environmental Impact Case Studies of Pharmaceutical Manufacturing Wastes (continued)

SITE	FACILITY	EXPOSURE		IMPACTS
		ENVIRONMENT	BIOTA/EFFECT	
Whitmoyer Laboratories, Jackson, Pennsylvania	Former site of an animal arsenical pharmaceutical facility from 1934-1984	Toxics in soil, groundwater, surface water, sediment, and possibly air. On-site contamination consists of arsenic, anile, 1,1-trichloroethane and trans-1,2-dichloroethane in groundwater; arsenic in soil and surface water. Off-site contamination consists of these compounds in groundwater from an industrial well, surface water and sediment.	Population Exposure.	In 1964, a groundwater plume of arsenic was identified. Residential wells got contaminated, and at least two people were hospitalized with chronic arsenic poisoning as a result of drinking contaminated well water. In 1988 there was an EPA immediate operation underway of bottled water and carbon filters were given to 20 homes and a water supply line was designed.
Department of Occupational and Environmental Health, St. Michael's Hospital, University of Toronto	Pharmaceutical Manufacturing Plant	--	Worker exposure to airborne sodium benzoate (SB).	Three workers complained of burning and itching about 15-30 minutes after exposure to SB dust, which lasted for approximately 45 - 120 minutes. The workers developed transient urticaria related to skin contamination with SB.

Table 28. Environmental Impact Case Studies of Pharmaceutical Manufacturing Wastes (continued)

SITE	FACILITY	EXPOSURE		IMPACTS
		ENVIRONMENT	BIOTA/EFFECT	
General Research Study	Pharmaceutical Industry	Airborne toxic chemicals (e.g., dust).	Worker exposure (hormone and antibiotics production workers).	Male workers exposed to estrogens may develop symptoms of monolateral or bilateral true gynaecomastia; in female workers, menstrual disorders, menorrhagia, hyperplasia of the endometrium and metrorrhagia during menopause. Male workers exposed to progestogens may develop diminution of libido, ejaculation praecox, testicular pain, tumefaction of the spermatic cord. Female workers exposed to androgens may develop menstrual and ovarian function disorders, diminished fertility, increased frequency of spontaneous abortions and symptoms of virilism. Workers exposed to antibiotics may develop pronounced leukopenia, discreet thrombocytopenia, hypovitaminosis, and phenomena of antibiotic resistance.
Association of Metropolitan Sewage Agencies	Pharmaceutical Industry	Organic pollutants in receiving wastewaters from pharmaceutical facilities	POTW operations interference and worker exposure (sewer)	AMSA members request EPA's assistance in regulating industry. Establishment of local limits is too complex, costly, technically difficult, and may be unenforceable. Treatment plant upsets and discharge of flammables are of concern.

Table 28. Environmental Impact Case Studies of Pharmaceutical Manufacturing Wastes (continued)

SITE	FACILITY	EXPOSURE		IMPACTS
		ENVIRONMENT	BIOTA/EFFECT	
Anne Arundel County, Maryland	Kansasco	High concentration of methylene chloride in wastewater	Population exposure	In 1988, sewage service discontinued due to high concentrations of methylene chloride in discharge - 25 homes evacuated and 21 people hospitalized. In 1991, 7 spills occurred over 3-month period. Nearby residents complained of dizziness and nausea. Sewer service discontinued. Facility has 17-year history of environmental violations. Fined $60,000 in 1987 and $1,000/spill in 1991.

Sources: DIALOG data base (Enviroline, Pollution Abstracts, Aquatic Science Abstracts, Water Resources Abstracts), 1990/1992 State Water Quality Assessments (305(b) Reports), Pharmaceutical Outreach Questionnaire (February 1993), correspondence from Association of Metropolitan Sewerage Agencies (February 1995) Washington Post (April 1992), Baltimore Evening Sun (January 1988, July 1991).

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