*Canadian Environmental Protection Act, 1999*

# Follow-up Report on a PSL1 Substance for Which Data Were Insufficient to Conclude Whether the Substance Was "Toxic" to Human Health

## Aniline

October 2002

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| | |
|---|---|
| CAS | Chemical Abstracts Service |
| CEPA 1988 | *Canadian Environmental Protection Act* |
| CEPA 1999 | *Canadian Environmental Protection Act, 1999* |
| kg-bw | kilogram body weight |
| $K_{ow}$ | octanol/water partition coefficient |
| LOAEL | Lowest-Observed-Adverse-Effect Level |
| LOEL | Lowest-Observed-Effect Level |
| NOAEL | No-Observed-Adverse-Effect Level |
| PSL1 | first Priority Substances List |
| $TD_{05}$ | dose associated with a 5% increase in tumour incidence |
| TDI | Tolerable Daily Intake |
| $TDL_{05}$ | 95% lower confidence limit of the $TD_{05}$ |

## SYNOPSIS

Although aniline is not produced in Canada, aniline and aniline hydrochloride are imported for use primarily as intermediates in the production of chemicals for the synthesis of rubber and polymers. The amounts imported are expected to decline as other substances replace aniline.

Aniline was included on the first Priority Substances List (PSL1) under the 1988 *Canadian Environmental Protection Act* (CEPA 1988) for assessment of potential risks to the environment and human health. As outlined in the Assessment Report released in 1994, relevant data identified before June 1993 were considered insufficient to conclude whether aniline was "toxic" to human health under Paragraph 11(c) of CEPA 1988.

Limited data relevant to estimation of exposure of the population of Canada have become available during the period following the release of the PSL1 assessment and prior to December 2000. However, the limited available monitoring data, most of which are considered to be semi-quantitative, are sufficient only as a basis for development of upper bounding estimates of exposure for the general population. These uncertain estimates exceed the Tolerable Daily Intake.

Based on the limited available data, it is proposed that there is reason to suspect that aniline is "toxic" to human health.

Additional information as a basis of estimation of exposure would permit more definitive conclusion under CEPA. Therefore, companies using aniline are invited to self identify and provide relevant data to permit additional assessment and more definitive conclusion of "toxic" or not considered to be "toxic". **If no relevant information is received, it is proposed that the Ministers of Environment and of Health consider the compound "toxic" as defined in Paragraph 64(c) of the Canadian Environmental Protection Act, 1999.**

## 1.0 INTRODUCTION

A common Introduction, which describes the process for the preparation of the updates of the Assessment Reports for the seven substances (including aniline) on the first Priority Substances List (PSL1) for which data were considered insufficient to conclude whether the substances were "toxic" to human health under the 1988 *Canadian Environmental Protection Act* (CEPA 1988), is posted on all web sites where the Assessment Reports appear.[1]

The strategy for the literature search to identify critical new data (including commercial activity in Canada, human exposure and effects) on aniline is presented in Appendix A of this Assessment Report. Only relevant data acquired prior to December 2000 were considered in the determination of whether aniline is "toxic" to human health under Paragraph 64(c) of the *Canadian Environmental Protection Act, 1999* (CEPA 1999).[2]

## 2.0 SUMMARY OF THE HUMAN HEALTH RISK ASSESSMENT FOR ANILINE CONDUCTED UNDER CEPA 1988 (BASED ON INFORMATION IDENTIFIED UP TO JUNE 1993) (GOVERNMENT OF CANADA, 1994)

At the time of release of the PSL1 assessment, aniline (Chemical Abstracts Service [CAS] No. 62-53-3; $C_6H_7N$) was not produced in Canada. Aniline and aniline hydrochloride were imported for use primarily as intermediates in the production of chemicals for the synthesis of rubber and polymers, although the amounts imported were expected to decline as aniline was replaced by other substances. An estimated 1.1 tonnes of aniline were released into the Canadian environment each year from various stages of its commercial life cycle but were not expected to persist. In the United States, aniline was used in the agricultural, dye, photographic chemical and pharmaceutical industries, including the manufacture of sulpha drugs, acetanilide, sweetening agents, hydroquinone, optical whitening agents, resins, marking inks, perfumes and shoe polishes. Derivatives of aniline were also used in the United States as herbicides, fungicides, insecticides, animal repellents and defoliants.

Data on concentrations of aniline in the principal media of exposure for the general population of Canada were not available. Rather, deterministic estimates of the average daily intake were developed based on (limited) identified monitoring data for ambient air in the United States, food in Germany and mainstream cigarette smoke and on lack of detection of aniline in drinking water in the province of Quebec. Data on the concentrations of aniline in breast milk, indoor air or soil in Canada (or elsewhere) were not identified.

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[1] See "Introduction to Assessment Reports for Reconsideration of PSL1 Substances for Which Data Were Insufficient to Conclude Whether the Substances Were 'Toxic' to Human Health (Paragraph 11(c), CEPA 1988; Paragraph 64(c), CEPA 1999)" at the following web sites: http://www.ec.gc.ca/substances/ese/eng/psap/PSL1_IIC.cfm or www.hc-sc.gc.ca/hecs-sesc/exsd/ps11.htm

[2] The potential impact of preliminary results of an additional monitoring study conducted by Health Canada (2002) is also considered.

These estimates of intake, which were based primarily on early data from other countries, differed from those developed on the basis of Level III fugacity modelling of concentrations in air, water and soil in southern Ontario by approximately seven orders of magnitude. These latter values were based on information more relevant to estimation of exposure of the Canadian population to aniline, including amounts imported into Canada (in 1989) and estimated release in southern Ontario, although such modelled estimates are considerably less certain than monitoring data.

At the time of release of the Assessment Report for aniline under CEPA 1988, available epidemiological studies in humans were inadequate to serve as a basis for assessment of the carcinogenicity of aniline. Based on the results of identified chronic studies in experimental species, aniline induced splenic tumours in male (but not female) rats at high doses; no such tumours were observed in male or female mice. The interspecies and sex-related variations in response in the two most extensive carcinogenesis bioassays were consistent with the greater metabolism of aniline by detoxification pathways in mice than in rats, the saturation of this pathway in rats at higher doses and observed sex-related differences in metabolism. The increased incidence of splenic tumours in male rats (at doses that may saturate the detoxification pathway) was associated with cellular damage. Hence, the induction of these tumours was considered potentially a consequence of enhanced cellular proliferation associated with cell damage resulting from the accumulation of damaged erythrocytes within this tissue. Data on the genotoxicity of aniline were mixed but consistent with this hypothesis, since aniline had not been genotoxic in the spleen, although this observation was based on limited data.

A Tolerable Daily Intake (TDI) (i.e., the level of intake to which it is believed that a person may be exposed daily over a lifetime without deleterious effects) of 1.4 µg/kg-bw per day was derived, therefore, for non-neoplastic effects. This value was based on the lowest dose of aniline (Lowest-Observed-Adverse-Effect Level [LOAEL] = 7.2 mg/kg-bw per day) at which adverse effects (increased splenic hemosiderin, extramedullary hematopoiesis and congestion in male CD-F rats) were observed, in the only available long-term animal study in which an adequate range of endpoints had been examined (CIIT, 1982), divided by an uncertainty factor of 5000 (×10 for intraspecies variation; ×10 for interspecies variation; ×10 for use of a LOAEL rather than a No-Observed-Adverse-Effect Level [NOAEL]; ×5 for limited evidence of carcinogenicity). For comparison, this value for the TDI is similar to that which could be derived (4.2 µg/kg-bw per day) based on the results of a (limited) clinical study on formation of methemoglobin in volunteers exposed by ingestion (Jenkins *et al*., 1972). This clinical study was considered inadequate in itself to serve as a basis for development of a TDI, since it was a short-term investigation of a limited range of biochemical effects in a very small number of subjects.

The highly uncertain estimates of exposure to aniline, which were based primarily on early data from other countries, and their considerable variation with modelled values (inherently

more uncertain but based on more relevant information on import and release in Canada) precluded meaningful comparison with the TDI.

**Therefore, data were considered insufficient to conclude whether aniline was "toxic" as defined under Paragraph 11(c) of CEPA 1988.**

## 3.0 POST-PSL1 ANALYSIS (BASED ON INFORMATION IDENTIFIED BETWEEN JUNE 1993 AND DECEMBER 2000)

### 3.1 Production, importation, use and release

Aniline is still not manufactured in Canada, and its importation has declined (i.e., from 0.9 kilotonnes in 1985 to 0.04 kilotonnes in 1999), primarily due to its replacement by other chemicals in the manufacture of rubber. The quantity of aniline projected to be imported into Canada in 2002 is 0.03 kilotonnes (CIS, 2001). Currently, the only major buyer of aniline in Canada is Uniroyal Chemical Company in Elmira, Ontario, where aniline is used primarily for research and development (CIS, 2001).

The most recent information from the National Pollutant Release Inventory (Environment Canada, 2000a) indicates that in 1998, 0.03 tonnes of aniline were emitted to air in Canada (as fugitive releases) by Dupont Canada Inc. in Ontario, while 2.9 tonnes were released for disposal (primarily by underground injection) by the Uniroyal Chemical Company in Ontario.

Aniline has not been registered as an active ingredient or as a formulant in pest control products in Canada, although a derivative of aniline (i.e., acid blue #25, aniline) is currently used in two registered products (Health Canada, 2000). Aniline is a component of several agricultural herbicides (e.g., Fenuron, Propham, Siduron) used in the United States, Western Europe and Japan (OECD, 2000).

### 3.2 Population exposure

Recent data relevant to estimation of exposure of the general population in Canada to aniline are limited. These include results of analyses of a composite sample[3] from 757 randomly selected single family homes across Canada for which analytical recovery was poor; the mean reported concentration was 104 μg/m$^3$ (Otson *et al*., 1994). Aniline was also not detected (limit of detection 0.3 mg/kg dry weight) in agricultural soil collected from nine provinces across

[3] Aliquots of individual 24-hour air sample extracts from each residence, which had been stored for 6–18 months, were pooled to form a composite exposure sample. The analytical recovery for the composite air sample was only 2%. The reported mean concentration of 104 μg/m$^3$ was corrected for this 2% recovery. In a more recent study by Health Canada (2002) with improved methodology but for which only preliminary results are available, mean concentrations of aniline in ambient air (n=24) ranged from 0.007 – 0.011μg/m$^3$. Mean levels in indoor air in smoking and non-smoking homes in urban and rural locations in Ontario (n=69) ranged from 0.008 to 0.035 μg/m$^3$.

Canada, including where there had been repeated heavy use of agricultural pesticides at intensively cropped farms (Webber and Wang, 1995). In recent studies, aniline was detected at concentrations ranging from 0.05 to 5.2 ppb (µg/L) in samples (n = 31) of breast milk collected from (smoking and non-smoking) women residing in Ontario; there was no significant difference in levels between smoking and non-smoking women (DeBruin *et al*., 1999). Identified recent monitoring data for foodstuffs are limited to the results of a field study (conducted in the United States) of the uptake by food crops of industrial organic contaminants. In this investigation, aniline was not detected (limit of detection 4 mg/kg) in corn, cabbage or carrots grown in sludge-treated soil (Webber *et al*., 1994).

Data on the aniline content of adhesives, dyes and rubber, which may contain residual amounts of aniline (OECD, 2000), were not identified.

Methodology for exposure assessment has evolved since completion of the PSL1 assessment. Deterministic estimates of total daily intake of aniline for six age groups (compared with five groups, previously) of the population of Canada, which incorporate these developments in methodology (EHD, 1998) and the more recent monitoring data mentioned above, are presented in Table 1. The assumptions on which these estimates are based are delineated in footnotes to the table.

Upper bounding estimates of total daily intakes of aniline for six distinct age groups of the general population range from 22µg/kg-bw per day (for seniors) to 85 µg/kg-bw per day (for children aged 6 months to 4 years).

## 3.3 Hazard characterization and dose–response analyses

### *3.3.1 Hazard characterization*

Additional toxicological data on aniline or aniline hydrochloride identified in the period since the PSL1 assessment was released (and prior to December 2000) include the results of *in vivo* genotoxicity studies in which DNA damage was observed in the organs of rodents exposed to a single oral dose (Sasaki et al., 2000), and increased micronuclei in the erythrocytes of mice exposed orally for 90 days (Witt et al., 2000). In *in vitro* studies, results were negative for induction of micronuclei or transformation in Syrian hamster embryo cells (Fritzenschaf et al., 1993) and mutagenicity in the Ames assay (Assman et al., 1997; Chung et al., 1995, 1996; Brennan and Schiestl, 1997) and *umu* test (Oda et al., 1995) in *S. typhimurium.* In contrast, results were positive for induction of homologous interchromosomal recombination (Vogel and Nivard, 1993) and nondisjunction (Munoz and Barnett, 1998) in *Drosophila*, chromosomal abberrations in Chinese hamster ovary cells (Chung et al., 1995, 1996), micronuclei in Chinese hamster lung cells (Matsushima et al.1999), and intrachromosomal recombination in *S. cerivisiae* (Brennan and Schiestl, 1997).

Relevant human data were restricted to the results of (limited) epidemiological studies in which

workers were exposed to aniline and other chemicals (Sorahan and Pope, 1993; Mikoczy *et al*., 1996; Alguacil et al., 2000; Sathiakumar and Deizell, 2000). In a recent update of the cohort study by Sorahan and Pope (1993), additional data analyses indicated no association between duration of employment in the aniline department and increased risk of bladder cancer in chemical production workers (Sorahan et al., 2000).

Additional repeated-dose toxicity studies conducted in experimental species are restricted to one subchronic study in which male Sprague-Dawley rats were exposed to a single concentration of aniline hydrochloride in drinking water for 90 days (Khan *et al*., 1993). Although the subchronic study by Khan *et al.* (1993) was considered inadequate for characterization of exposure–response, the results of this investigation are similar to those of other repeated-dose toxicity studies in which the blood and spleen have been identified as critical tissues for toxicological effects of aniline.

### *3.3.2 Dose–response analyses*

In view of the absence of critical recent toxicological data, the dose–response analyses presented here reflect primarily those developed in the PSL1 assessment released under CEPA 1988. In addition, estimates of carcinogenic potency have been developed, consistent with increasing weight of evidence of genotoxicity.

#### 3.3.2.1 Oral exposure

In the assessment of aniline for PSL1, non-neoplastic histopathological lesions in the spleen of rats (the most sensitive rodent species) were considered to be the critical endpoint for characterization of dose–response. Since the cytotoxicity of aniline (associated with the saturation of the principal detoxification pathway) may be the crucial determinant in the carcinogenicity of this compound in the spleen of rats (but not mice) at high doses, measures of dose–response for non-neoplastic effects may be protective for tumours, although this conclusion is uncertain.

Data relevant to characterization of the mode of induction of tumours are limited. The results of genotoxicity studies are equivocal, with results of several recent *in vivo* assays being positive. There is also some indication in *in vivo* studies that aniline may interact directly with DNA in the spleen of rats (but not mice), although DNA binding in the spleen is low compared with that in other tissues (McCarthy *et al*., 1985). In view of uncertainty concerning the mode of induction of tumours, therefore, measures of cancer potency are also presented here and compared with those for non-cancer effects.

Estimates of carcinogenic potency ($TD_{05}$, the dose associated with a 5% increase in tumour incidence above controls) for aniline have been derived based on the incidence of splenic tumours (stromal sarcoma, hemangiosarcoma, fibrosarcoma, osteogenic sarcoma and capsular sarcoma) in control and three dose groups of CD-F rats exposed in the diet to 10–100 mg aniline

hydrochloride/kg-bw per day (7.2–71.9 mg aniline/kg-bw per day) for up to 104 weeks (CIIT, 1982). This investigation was considered the most appropriate for quantitative assessment of the $TD_{05}$, since it was the only identified long-term study in which an adequate range of endpoints was examined in the most sensitive rodent species. In addition, compared with the NCI (1978) bioassay, there were more dose groups (three dose groups and controls vs. two dose groups) in this study, as well as larger numbers of animals per group (n = 130 per sex vs. n = 50 males) and more extensive histopathological examination.

Measures of tumorigenic potency have been developed, based on multistage modelling of incidence using GLOBAL 82 (Howe and Crump, 1982). The incidences of tumours on which the estimates of potency are based, degrees of freedom, parameter estimates and nature of any adjustments for mortality or period of exposure are presented in Table 2 and Figure 1. The lowest calculated $TD_{05}$ is 46 mg/kg-bw per day, based on stromal sarcoma in the spleen of male rats; the lower 95% confidence limit ($TDL_{05}$) for this value is 35 mg/kg-bw per day. The most conservative estimate of carcinogenic potency (i.e., the $TDL_{05}$ of 35 mg/kg-bw per day) is one order of magnitude greater than the LOAEL (7.2 mg/kg-bw per day) that formed the basis of the calculated estimate for non-cancer effects.

Estimates of the total daily intake of aniline for the general population of Canada, which range from 22 to 85 µg/kg-bw per day for the various age groups, are one order of magnitude greater than the TDI (1.4 µg/kg-bw per day) calculated for non-neoplastic effects (see Section 2.0). However, the bounding estimates of exposure for the general population are highly uncertain, owing to the considerable limitations of the available monitoring data, many of which can be considered to be semi-quantitative only. For example, intake from food was based primarily on analysis of a limited number of foodstuffs in an early study in another country (Germany), for which methodology was inadequately documented (Neurath *et al.*, 1977).

3.3.2.2 Inhalation

Available data are considered inadequate to meaningfully characterize exposure–response for the effects of aniline following inhalation. In a single identified long-term inhalation study, minimal effects (mild cyanosis, a slight [unspecified] reduction in body weight and a slight [statistical evaluation not presented] increase in methemoglobin) were reported in male Wistar rats exposed (whole body) to a single concentration (19 $mg/m^3$) of aniline for 26 weeks (Oberst *et al*., 1956).

## 3.4 Human health risk characterization

Highly uncertain bounding estimates of total daily intakes of aniline from all media (i.e., ambient air, indoor air, soil, drinking water, food and mainstream cigarette smoke) for the general population of Canada exceed the TDI (1.4 µg/kg-bw per day) for non-neoplastic effects. Indeed,

for all age groups, intakes of aniline in each of indoor air, ambient air or food exceed the value of the TDI by up to 40-fold.[4]

Based on the limited available data, therefore, there is reason to suspect that aniline is "toxic" to human health.

### 3.5 Uncertainties and degree of confidence in human health risk characterization

Confidence in the levels of aniline in food is considered to be low. Intake from this source was estimated based primarily on a limited (early) investigation of a small number of fruits and vegetables from another country (Germany) (Neurath *et al.*, 1977), in which reporting of the protocol and results is considered inadequate. Limitations of the principal study include lack of reporting of the recovery efficiency or reproducibility of the methods, absence of information concerning the use of correction factors, chromatographic retention times or limit of detection, and the apparent absence of an aniline standard for mass spectrometry. The elevated levels of aniline detected in foods (e.g., 30.9 mg/kg in carrots) in this survey conflict with those of the more recent study by Webber *et al*. (1994), in which aniline was not detected (e.g., <4 mg/kg in carrots) in a small number of vegetables grown in sludge-treated soil in the United States.

There is a relatively high degree of certainty that consumption of drinking water and consumption of soil do not contribute significantly to the intake of aniline by Canadians, based on sensitive measurements of drinking water and agricultural soil collected from several sources in Canada, in which aniline was consistently not detected.

The degree of confidence in the database on toxicity that serves as the basis for the development of the TDI is moderate, although there is a relatively high degree of certainty that the critical effects following ingestion are those that occur in the spleen. Available data on effects of aniline following inhalation are also inadequate to characterize exposure–response.

### 3.6 Considerations for follow-up (further action) and Conclusion

Additional information is being requested as a basis for concluding whether the compound can be considered to be "toxic" or "not toxic" under CEPA. **If no relevant information is received, it is proposed that the Ministers of Environment and of Health consider the compound to be "toxic" as defined in Paragraph 64(c) of the *Canadian Environmental Protection Act*, *1999*.**

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4 While preliminary results from a more recent (Health Canada 2002) study indicate that intake of aniline from indoor and ambient air in Canada is negligible, for all age groups, estimated intake of aniline in food alone exceeds the value of the TDI by up to 13-fold.

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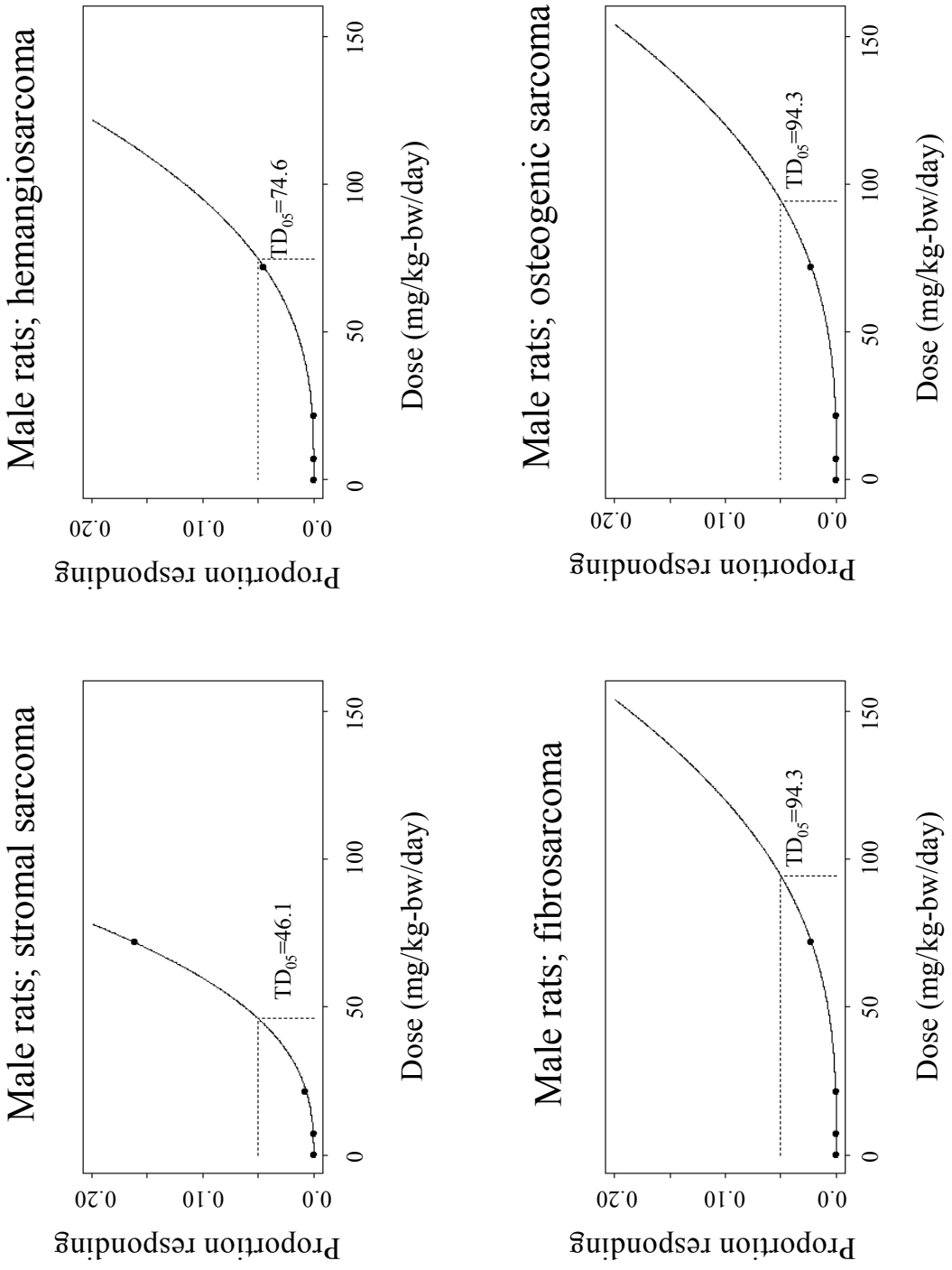
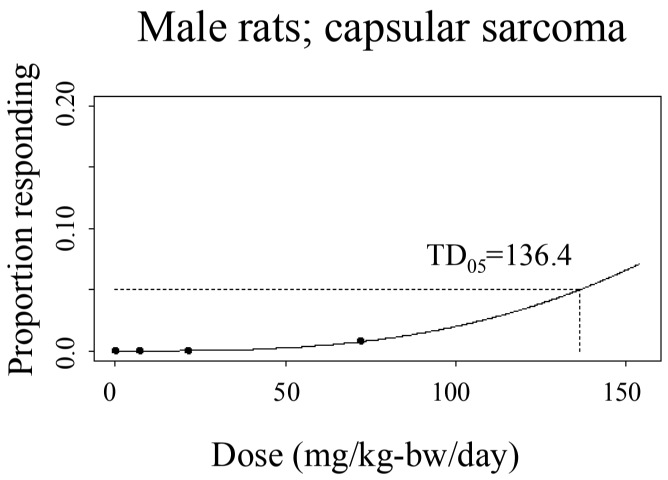
**Figure 1:** Cancer potency estimates ($TD_{05}$s) based on splenic tumours in rats




Male rats; capsular sarcoma
Proportion responding
0.0
0.10
0.20
TD05=136.4
0
50
100
150
Dose (mg/kg-bw/day)

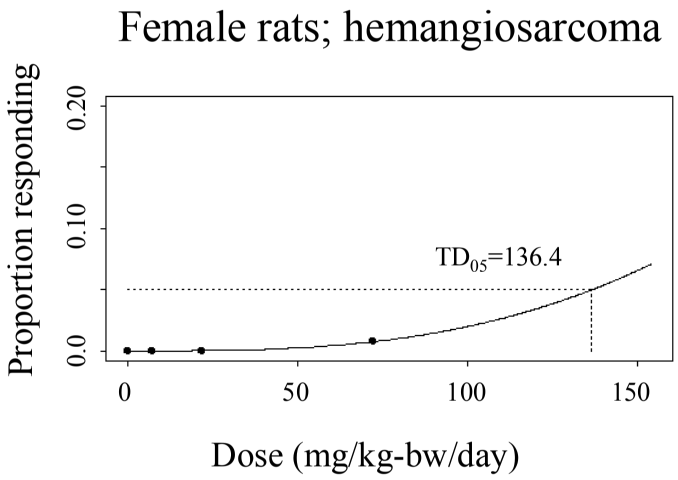

Female rats; hemangiosarcoma
Proportion responding
0.0
0.10
0.20
TD05=136.4
0
50
100
150
Dose (mg/kg-bw/day)

**Table 1:** Worst-case estimates of total daily intake of aniline for the general population of Canada

| Medium | Estimated intake (µg/kg-bw per day) | | | | | |
|---|---|---|---|---|---|---|
| | **0–6 months[1]** | **6 months–4 years[2]** | **5–11 years[3]** | **12–19 years[4]** | **20–59 years[5]** | **60+ years[6]** |
| Ambient air[7] | 0.18–5.9 | 0.38–12.8 | 0.29–9.9 | 0.17–5.7 | 0.14–4.9 | 0.12–4.2 |
| Indoor air[8] | 25.5 | 54.6 | 42.6 | 24.2 | 20.8 | 18.0 |
| Drinking water[9] | $1.3 \times 10^{-2}$ | $6.45 \times 10^{-3}$ | $6.45 \times 10^{-3}$ | $3.37 \times 10^{-3}$ | $2.82 \times 10^{-3}$ | $2.77 \times 10^{-3}$ |
| Food[10] | 0.01–5.1[11] | 16.8–17.9 | 9.8–10.4 | 5.2–5.4 | 4.6–4.7 | 4.2–4.3 |
| Soil[12] | 0.001 | 0.002 | 0.001 | 0.0002 | 0.0001 | 0.0001 |
| Cigarette smoke[13] | – | – | – | – | 0.04 | 0.03 |
| **Total intake** | **25.7–36.5** | **71.8–85.3** | **52.7–62.9** | **29.6–35.3** | **25.6–30.4** | **22.4–26.5** |

1 Assumed to weigh 7.5 kg, breathe 2.1 $m^3$ of air per day, consume 30 mg of soil per day and drink 0.2 L of water per day (EHD, 1998).

2 Assumed to weigh 15.5 kg, breathe 9.3 $m^3$ of air per day, consume 100 mg of soil per day and drink 0.2 L of water per day (EHD, 1998).

3 Assumed to weigh 31.0 kg, breathe 14.5 $m^3$ of air per day, consume 65 mg of soil per day and drink 0.4 L of water per day (EHD, 1998).

4 Assumed to weigh 59.4 kg, breathe 15.8 $m^3$ of air per day, consume 30 mg of soil per day and drink 0.4 L of water per day (EHD, 1998).

5 Assumed to weigh 70.9 kg, breathe 16.2 $m^3$ of air per day, consume 30 mg of soil per day and drink 0.4 L of water per day (EHD, 1998).

6 Assumed to weigh 72.0 kg, breathe 14.3 $m^3$ of air per day, consume 30 mg of soil per day and drink 0.4 L of water per day (EHD, 1998).

7 Based on the range of concentrations of aniline (0.005–0.17 mg/$m^3$) in ambient air in suburban and industrial sites in the United States (Shah and Hyerdahl, 1988) and an estimated 3 hours per day spent outdoors (EHD, 1998).

8 Based on a reported mean concentration of 104 µg aniline/$m^3$ in the indoor air of 757 single family homes in 10 Canadian provinces surveyed during 1991 (aliquots of individual 24-hour air sample extracts, which had been stored for 6–18 months, were pooled to form a composite exposure sample; Otson *et al*., 1994) and an estimated 21 hours per day spent indoors (EHD, 1998).

9 Based on the limit of detection (i.e., 0.5 µg/L) reported in a survey of drinking water conducted (in 1991) in 17 municipalities in Quebec, in which aniline was not detected (Quebec Ministry of the Environment, 1992).

10 Based on measured concentrations of aniline (0.1–22 mg/kg) in fresh and preserved fruit and vegetables (cauliflower, beets, radish, rhubarb, celery, lettuce, apple, green beans)

collected from retail outlets in Germany (Neurath *et al*., 1977), the limit of detection (4 mg/kg dry weight) of aniline in a survey in which this compound was not detected in corn, cabbage or carrots grown in sludge-treated soil in the United States (Webber *et al*., 1994) and the daily consumption of these foods by the various age groups of the general population of Canada (EHD, 1998).

[11] Based on the range of concentrations of aniline (0.05–5.2 µg/L) in samples (n = 31) of breast milk from (smoking and non-smoking) women residing in Ontario (DeBruin *et al*., 1999), a daily consumption of 742 mL breast milk per day (as food) for infants and the assumption that infants in Canada are exclusively breast-fed (EHD, 1998).

[12] Based on the limit of detection (i.e., 0.3 mg/kg) of aniline in a survey of agricultural soil from nine provinces in Canada in which aniline was not detected (Webber and Wang, 1995). Samples included typical agricultural soils (n = 24) and additional soils (n = 6) subjected to repeated heavy use of agricultural pesticides.

[13] Based on the mean concentration of aniline (102 ng/cigarette) in mainstream smoke from cigarettes purchased in the United States (Patriankos and Hoffmann, 1979) and an estimated 20 cigarettes smoked per day (EHD, 1998).

**Table 2:** Tumorigenic doses ($TD_{05}$s and $TDL_{05}$s) for aniline based on the incidence of splenic tumours in male CD-F rats (CIIT, 1982)

| Tumour type | Aniline dose (mg/kg-bw per day) | Tumour incidence | $TD_{05}$ ($TDL_{05}$) (mg/kg-bw per day) | Parameter estimates |
|---|---|---|---|---|
| **Males** | | | | |
| Stromal sarcoma | 0 | 0/123 | 46 (35) | Chi-square = 0.08 |
| | 7.2 | 0/129 | | Degrees of freedom = 1 |
| | 21.6 | 1/128 | | p-value = 0.78 |
| | 71.9 | 21/130 | | |
| Hemangiosarcoma | 0 | 0/123 | 75 (61) | Chi-square = 0.17 |
| | 7.2 | 0/129 | | Degrees of freedom = 2 |
| | 21.6 | 0/128 | | p-value = 0.92 |
| | 71.9 | 6/130 | | |
| Fibrosarcoma | 0 | 0/123 | 94 (72) | Chi-square = 0.08 |
| | 7.2 | 0/129 | | Degrees of freedom = 2 |
| | 21.6 | 0/128 | | p-value = 0.95 |
| | 71.9 | 3/130 | | |
| Osteogenic sarcoma | 0 | 0/123 | 94 (72) | Chi-square = 0.08 |
| | 7.2 | 0/129 | | Degrees of freedom = 2 |
| | 21.6 | 0/128 | | p-value = 0.96 |
| | 71.9 | 3/130 | | |
| Capsular sarcoma | 0 | 0/123 | 136 (89) | Chi-square = 0.03 |
| | 7.2 | 0/129 | | Degrees of freedom = 2 |
| | 21.6 | 0/128 | | p-value = 0.98 |
| | 71.9 | 1/130 | | |
| **Females** | | | | |
| Hemangiosarcoma | 0 | 0/129 | 136 (89) | Chi-square = 0.03 |
| | 7.2 | 0/129 | | Degrees of freedom = 2 |
| | 21.6 | 0/130 | | p-value = 0.99 |
| | 71.9 | 1/130 | | |

## APPENDIX A: SEARCH STRATEGY — NEW INFORMATION FOR THE ASSESSMENT OF "TOXIC" TO HUMAN HEALTH UNDER PARAGRAPH 64(C) OF CEPA 1999

To identify new critical exposure and toxicological data for aniline, an updated literature search was conducted in May 2000 using the strategy of searching by name or CAS registry number in the following databases: Canadian Research Index, CCRIS (Chemical Carcinogenesis Research Information System, U.S. National Cancer Institute; 1982–2000), HSDB (Hazardous Substances Data Bank, U.S. National Library of Medicine), IRIS (Integrated Risk Information System, U.S. Environmental Protection Agency) and RTECS (Registry of Toxic Effects of Chemical Substances, U.S. National Institute for Occupational Safety and Health). Its name and registry number were searched in the Toxline (U.S. National Library of Medicine; 1993–2000) and Medline (U.S. National Library of Medicine; 1993–2000) databases. A search was also conducted (up to December 2000) in the following Internet web sites: Agency for Toxic Substances and Disease Registry, International Agency for Research on Cancer, International Programme on Chemical Safety, Micromedix TOMES Plus System$^{TM}$ (composed of CHRIS, ERG2000, HAZARDTEXT, HSDB, INFOTEXT, IRIS, MEDITEXT, New Jersey Fact Sheets, NIOSH Pocket Guide, OHM/TADS and RTECS), National Toxicology Program, Organisation for Economic Co-operation and Development, and U.S. Environmental Protection Agency.

Information presented in a SIDS Initial Assessment Report (SIAR) for the Organisation for Economic Co-operation and Development (OECD, 2000), which included data on exposure and effects of aniline, was also reviewed.

An updated literature review (up to December 2000) of production, importation, use and environmental release data was based on a search of information in the National Pollutant Release Inventory (Environment Canada, 2000a), the Toxic Release Inventory (U.S. EPA, 2000), the Pesticide Management Regulatory Agency of Health Canada (Health Canada, 2000) and the Use Patterns and Controls Implementation Section of Environment Canada (Environment Canada, 2000b), as well as information provided under contract by Camford Information Services (CIS, 2001).