APPENDIX A. ATSDR MINIMAL RISK LEVELS AND WORKSHEETS

The Comprehensive Environmental Response, Compensation, and Liability Act (CERCLA) [42 U.S.C. 9601 et seq.], as amended by the Superfund Amendments and Reauthorization Act (SARA) [Pub. L. 99–499], requires that the Agency for Toxic Substances and Disease Registry (ATSDR) develop jointly with the U.S. Environmental Protection Agency (EPA), in order of priority, a list of hazardous substances most commonly found at facilities on the CERCLA National Priorities List (NPL); prepare toxicological profiles for each substance included on the priority list of hazardous substances; and assure the initiation of a research program to fill identified data needs associated with the substances.

The toxicological profiles include an examination, summary, and interpretation of available toxicological information and epidemiologic evaluations of a hazardous substance. During the development of toxicological profiles, Minimal Risk Levels (MRLs) are derived when reliable and sufficient data exist to identify the target organ(s) of effect or the most sensitive health effect(s) for a specific duration for a given route of exposure. An MRL is an estimate of the daily human exposure to a hazardous substance that is likely to be without appreciable risk of adverse noncancer health effects over a specified duration of exposure. MRLs are based on noncancer health effects only and are not based on a consideration of cancer effects. These substance-specific estimates, which are intended to serve as screening levels, are used by ATSDR health assessors to identify contaminants and potential health effects that may be of concern at hazardous waste sites. It is important to note that MRLs are not intended to define clean-up or action levels.

MRLs are derived for hazardous substances using the no-observed-adverse-effect level/uncertainty factor approach. They are below levels that might cause adverse health effects in the people most sensitive to such chemical-induced effects. MRLs are derived for acute (1–14 days), intermediate (15–364 days), and chronic (365 days and longer) durations and for the oral and inhalation routes of exposure. Currently, MRLs for the dermal route of exposure are not derived because ATSDR has not yet identified a method suitable for this route of exposure. MRLs are generally based on the most sensitive chemical-induced end point considered to be of relevance to humans. Serious health effects (such as irreparable damage to the liver or kidneys, or birth defects) are not used as a basis for establishing MRLs. Exposure to a level above the MRL does not mean that adverse health effects will occur.

MRLs are intended only to serve as a screening tool to help public health professionals decide where to look more closely. They may also be viewed as a mechanism to identify those hazardous waste sites that

are not expected to cause adverse health effects. Most MRLs contain a degree of uncertainty because of the lack of precise toxicological information on the people who might be most sensitive (e.g., infants, elderly, nutritionally or immunologically compromised) to the effects of hazardous substances. ATSDR uses a conservative (i.e., protective) approach to address this uncertainty consistent with the public health principle of prevention. Although human data are preferred, MRLs often must be based on animal studies because relevant human studies are lacking. In the absence of evidence to the contrary, ATSDR assumes that humans are more sensitive to the effects of hazardous substance than animals and that certain persons may be particularly sensitive. Thus, the resulting MRL may be as much as 100-fold below levels that have been shown to be nontoxic in laboratory animals.

Proposed MRLs undergo a rigorous review process: Health Effects/MRL Workgroup reviews within the Division of Toxicology, expert panel peer reviews, and agency-wide MRL Workgroup reviews, with participation from other federal agencies and comments from the public. They are subject to change as new information becomes available concomitant with updating the toxicological profiles. Thus, MRLs in the most recent toxicological profiles supersede previously published levels. For additional information regarding MRLs, please contact the Division of Toxicology, Agency for Toxic Substances and Disease Registry, 1600 Clifton Road NE, Mailstop F-32, Atlanta, Georgia 30333.

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

Chemical Name: α-HCH
CAS Number: 319-84-6
Date: June 2005
Profile Status: Final Post-Public Comment Draft
Route: [ ] Inhalation [X] Oral
Duration: [ ] Acute [ ] Intermediate [X] Chronic
Graph Key: 61
Species: Rat

Minimal Risk Level: 0.008 [X] mg/kg/day [ ] ppm

Reference: Fitzhugh OG, Nelson AA, Frawley JP. 1950. The chronic toxicities of technical benzene hexachloride and its α, β and γ isomers. J Pharmacol Exp Ther 100:59-66. (Table 2 of the article).

Experimental design: Groups of 10 male and 10 female Wistar rats were treated with 0, 10, 50, 100, or 800 ppm α-HCH in food for life. Estimated doses were 0, 0.7, 3.5, 7, or 56 mg/kg/day in males and 0, 0.8, 4, 8, or 64 mg/kg/day in females. The mean age at death was 54.6 weeks for the 10 ppm group (NOAEL) and 58.3 weeks for the control group. The lifetime of the animals sacrificed at the end of the experiment was taken as 107 weeks. End points included clinical signs, body weight, food consumption, organ weight, gross pathology, and histopathology.

Effects noted in study and corresponding doses: No exposure-related changes occurred at the low dose in either sex, indicating that the highest NOAEL is 0.8 mg/kg/day in females. Liver effects were qualitatively described in both sexes at higher doses, progressing from very slight histological changes with increased liver weight but no gross liver pathology at 3.5–4 mg/kg/day, slight histological changes with no gross pathology at 7–8 mg/kg/day, and moderate histological damage accompanied by moderate gross pathology at 56–64 mg/kg/day. The hepatic histopathological changes classified as moderate included hepatic cell atrophy, fatty degeneration, and focal necrosis. Non-hepatic effects included decreased body weight gain (18 and 13% less than controls in males and females), slight kidney histopathology (focal nephritis), and reduced lifespan (38% less than controls) at 56–64 mg/kg/day.

Dose and end point used for MRL derivation: 0.8 mg/kg/day (10 ppm); no hepatic effects.

[X] NOAEL [ ] LOAEL

Uncertainty Factors used in MRL derivation:

[ ] 10 for use of a LOAEL
[X] 10 for extrapolation from animals to humans
[X] 10 for human variability

Was a conversion used from ppm in food or water to a mg/body weight dose? Yes.
If so, explain: Food factor of 0.07 and 0.08 kg feed/kg body weight/day for male and female Wistar rats, respectively, were used to convert dose from ppm food to mg/kg body weight as follows:
10 ppm x 0.07 (male rat food factor) = 0.7 mg/kg/day; 50 ppm=3.5 mg/kg/day; 100 ppm=7 mg/kg/day; 800 ppm=56 mg/kg/day; 10 ppm x 0.08 (female rat food factor)=0.8 mg/kg/day; 50 ppm=4 mg/kg/day; 100 ppm=8 mg/kg/day; 800 ppm=64 mg/kg/day.

If an inhalation study in animals, list the conversion factors used in determining human equivalent dose: NA.

Other additional studies or pertinent information which lend support to this MRL: Other studies have observed various hepatic effects after chronic-duration oral exposure to α-HCH and other HCH isomers (Amyes et al. 1990; Ito et al. 1975; Kashyap et al. 1979; Munir et al. 1983; NCI 1977; Thorpe and Walker 1973; Wolff et al. 1987). Amyes et al. 1990 observed periacinar hypertrophy in male and female Wistar rats treated with 8 mg/kg/day γ-HCH in their diet for up to 52 weeks. The NOAEL was determined to be 0.8 mg/kg/day. Hepatocellular carcinoma was observed in rats fed 50 mg/kg/day α-HCH in their diet for 72 week (Ito et al. 1975). Hepatocellular carcinoma was also reported in mice treated with 34 mg/kg/day β-HCH in their diet for 104 weeks (Thorpe and Walker 1973).

Agency Contact (Chemical Manager): Alfred Dorsey, D.V.M.

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

Chemical Name: β-HCH
CAS Number: 319-85-7
Date: June 2005
Profile Status: Final Post-Public Comment Draft
Route: [ ] Inhalation [X] Oral
Duration: [X] Acute [ ] Intermediate [ ] Chronic
Graph Key: 10
Species: Mouse

Minimal Risk Level: 0.05 [X] mg/kg/day [ ] ppm

Reference: Van Velsen FL, Danse LHJC, Van Leeuwen FXR, et al. 1986. The subchronic oral toxicity of the β-isomer of hexachlorocyclohexane in rats. Fundam Appl Toxicol 6:697-712.

Experimental design: Groups of 10 male and 10 female Wistar rats were exposed to diets containing 0, 2, 10, 50, or 250 ppm β-HCH in food for 13 weeks and then sacrificed. Estimated dietary doses are 0, 0.18, 0.9, 4.5, or 22.5 mg/kg/day in males, and 0, 0.2, 1.0, 5, or 25 mg/kg/day in females. End points that were examined included clinical signs, body weight, food consumption, hematology, blood biochemistry, organ weights, gross pathology, and histopathology.

Effects noted in study and corresponding doses: At the end of week 2, two male and two female rats receiving the highest dose (22.5 and 25 mg/kg/day, respectively) exhibited clinical signs of ataxia and became progressively inactive. Within 3 days of the first signs of ataxia, the animals became comatose and were sacrificed

Dose and end point used for MRL derivation: 4.5 mg/kg/day; no reported signs of neurotoxicity (ataxia, inactivity, coma).

[X] NOAEL [ ] LOAEL

Uncertainty Factors used in MRL derivation:

[ ] 10 for use of a LOAEL
[X] 10 for extrapolation from animals to humans
[X] 10 for human variability

Was a conversion used from ppm in food or water to a mg/body weight dose? Yes.
If so, explain: A food factor of 0.1 kg feed/kg body weight/day for female Wistar rats was used to convert from ppm in food to mg/kg as follows: 2 ppm x 0.1 (rat food factor)=0.02 mg/kg/day; 10 ppm=1.0 mg/kg/day; 50 ppm=5.0 mg/kg/day; 250 ppm=25 mg/kg/day.

If an inhalation study in animals, list the conversion factors used in determining human equivalent dose: NA.

Other additional studies or pertinent information which lend support to this MRL: Support for neurotoxicity as the critical effect for acute oral exposure to β-HCH is provided by other studies of this isomer identifying the nervous system as a target of toxicity. Rats exposed to 66 mg/kg/day of β-HCH in food for 30 days (Muller et al. 1981) exhibited significantly reduced tail nerve motor conduction velocity.

Agency Contact (Chemical Manager): Alfred Dorsey, D.V.M.

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

Chemical Name: β-HCH
CAS Number: 319-85-7
Date: June 2005
Profile Status: Final Post-Public Comment Draft
Route: [ ] Inhalation [X] Oral
Duration: [ ] Acute [X] Intermediate [ ] Chronic
Graph Key: 25
Species: Rat

Minimal Risk Level: 0.0006 [X] mg/kg/day [ ] ppm

Reference: Van Velsen FL, Danse LHJC, Van Leeuwen FXR, et al. 1986. The subchronic oral toxicity of the β-isomer of hexachlorocyclohexane in rats. Fundam Appl Toxicol 6:697-712.

Experimental design: Groups of 10 male and 10 female Wistar rats were exposed to diets containing 0, 2, 10, 50, or 250 ppm β-HCH in food for 13 weeks and then sacrificed. Estimated dietary doses are 0, 0.18, 0.9, 4.5, or 22.5 mg/kg/day in males, and 0, 0.2, 1.0, 5, or 25 mg/kg/day in females. End points that were examined included body weight, food consumption, hematology, blood biochemistry, organ weights, gross pathology, and histopathology.

Effects noted in study and corresponding doses: Hepatic effects were observed that included hyalinization of centrilobular cells in males at ≥0.18 mg/kg/day and females at 25 mg/kg/day; increased absolute and relative liver weight in both sexes at ≥0.9 mg/kg/day in males and ≥1.0 mg/kg/day in females; periportal fat accumulation, increased mitosis and/or focal liver cell necrosis in males at ≥4.5 mg/kg/day and females at ≥5 mg/kg/day; and centrilobular hepatocytic hypertrophy, proliferation of smooth endoplasmic reticulum, increased microsomal activity, and/or increased glycogen content in males at 22.5 mg/kg/day and females at 25 mg/kg/day. Other systemic effects included increased absolute and/or kidney weight in females at ≥2.0 mg/kg/day and males at ≥4.5 mg/kg/day; renal medulla calcinosis in males at 22.5 mg/kg/day; and clinical signs (ataxia progressing to inactivity and coma), hematologic and splenic changes indicative of anemia (decreased red blood cells and hemoglobin, increased extramedullar hematopoiesis), and reduced body weight in males at 22.5 mg/kg/day and females at 25 mg/kg/day. Due to the dose-related nature and progression in severity of the hepatic effects, and the mild, reversible nature of the changes at the lowest dose level, 0.18 mg/kg/day is considered to be a minimal LOAEL based on hyalinization of centrilobular cells, which indicates the inititation of hepatic effects. The liver is an established target of β-HCH in other subchronic and chronic studies in rats and mice (Fitzhugh et al. 1950; Ikegami et al. 1991a, 1991b; Ito et al. 1973; Schoter et al. 1987).

Dose and end point used for MRL derivation: 0.18 mg/kg/day; hyalinization of centrilobular cells.

[ ] NOAEL [X] LOAEL

Uncertainty Factors used in MRL derivation:

[X] 3 for use of a minimal LOAEL
[X] 10 for extrapolation from animals to humans
[X] 10 for human variability

Was a conversion used from ppm in food or water to a mg/body weight dose? Yes.
If so, explain: A food factor of 0.09 kg feed/kg body weight/day for male Wistar rats was used to convert from ppm in food to mg/kg as follows: 2 ppm x 0.09 (rat food factor)=0.18 mg/kg/day; 10 ppm=0.9 mg/kg/day; 50 ppm=4.5 mg/kg/day; 250 ppm=22.5 mg/kg/day.

If an inhalation study in animals, list the conversion factors used in determining human equivalent dose: NA.

Other additional studies or pertinent information which lend support to this MRL: Significant increases in liver weight and the levels of hepatic cytochrome P-450, triglycerides, phospholipids, and cholesterol were seen in rats fed 50 mg/kg/day β-HCH for 2 weeks (Ikegami et al. 1991a, 1991b). Liver hypertrophy was seen in rats fed 25 mg/kg/day for 24 weeks (Ito et al. 1975), and in mice fed 32.5 mg/kg/day for 24 weeks (Ito et al. 1973). Fatty degeneration and necrosis were seen in liver of rats fed 0.5–40 mg/kg/day for up to 53 weeks (Fitzhugh et al. 1950). Schöter et al. (1987) also observed an increase in hepatic foci in rats exposed to 3 mg/kg/day in the diet for 20 weeks.

Agency Contact (Chemical Manager): Alfred Dorsey, D.V.M.

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

Chemical Name: γ-HCH
CAS Number: 58-89-9
Date: June 2005
Profile Status: Final Post-Public Comment Draft
Route: [ ] Inhalation [X] Oral
Duration: [X] Acute [ ] Intermediate [ ] Chronic
Graph Key: 23
Species: Rat

Minimal Risk Level: 0.003 [X] mg/kg/day [ ] ppm

Reference: Dalsenter PR, Faqi AS, Webb J, et al. 1997b. Reproductive toxicity and toxicokinetics of lindane in the male offspring of rats exposed during lactation. Hum Exp Toxicol 16:146-153.

Experimental design: Reproductive toxicity was evaluated in male offspring of groups of 9 Bor:spf female rats that were administered γ-HCH in peanut oil by gavage as a single 6 mg/kg dose on day 9 or day 14 of lactation, or as daily 1 mg/kg/day doses on days 9-14 of lactation (Dalsenter et al. 1997b). A group of 9 controls was administered the vehicle alone on days 9-14 of lactation. Male offspring (10 or 20/group) were terminated on postnatal day (pnd) 65 (puberty) or 140 (adulthood) and evaluated for the following end points: testis and epididymis weights, spermatid and sperm numbers, serum testosterone level, sexual behavior at 130 days of age during 1:1 mating with unexposed females (mount latency, intromission and ejaculatory latency, number and frequency of intromissions), mating index (number sperm positive females/number males mated x100), pregnancy index (number of males that made females pregnant/number of males that made females sperm-positive x100), fertility index (number of days elapsed until males fertilized their female partner), pregnancy end points (numbers of litters, implantations/litters, fetuses/litter, resorptions), and testicular histology (6 mg/kg offspring only).

Effects noted in study and corresponding doses: Effects occurred in all treated groups. Findings in the 1 mg/kg/day offspring included statistically significant ($p<0.05$) reductions in relative testicular weight at pnd 140 (6.4% less than controls), relative epididymis weight at pnd 65 (7.1%), spermatid number at pnd 65 and 140 (29.0 and 12.8%, respectively), sperm number at pnd 140 (13.2%), serum testosterone at pnd 65 (30.0%), and increased number of intromissions per minute up to ejaculation at pnd 130 (45%). Effects were generally similar in type and magnitude in the 6 mg/kg offspring following exposure on gestation day 9 or 14, including significantly reduced relative testicular weight at pnd 65 and 140 (~10%), spermatid and sperm numbers at pnd 140 (~8–10%), and serum testosterone at pnd 140 (~50%). There were no significant effects on sexual behavior or fertility in the 1 mg/kg/day or 6 mg/kg offspring as shown by the mating, pregnancy, and fertility indices or other pregnancy end points. Thus, the significant changes observed for relative organ weights, sperm number, hormone levels, and intromission incidence are considered minimally effective for reproduction; their associated dose levels are considered minimal LOAELs. The testicular histological examinations of the 6 mg/kg/day offspring showed large areas of normal tissue, although some areas had distinct changes ranging from small alterations to a pronounced effect. The most affected areas were the tubules in which the effects included necrotic changes and reductions in Leydig cell numbers and spermatogenesis.

Concentration and end point used for MRL derivation: 1 mg/kg/day LOAEL for developmental/reproductive effects in male offspring exposed during lactation.

Calculations: 1 mg/kg/day x 1/300 UF = 0.003 mg/kg/day.

[ ] NOAEL [X] LOAEL

Uncertainty Factors used in MRL derivation:

[X] 3 for use of a minimal LOAEL
[X] 10 for extrapolation from animals to humans
[X] 10 for human variability

Was a conversion factor used from ppm in food or water to a mg/body weight dose? No.

If an inhalation study in animals, list conversion factors used in determining human equivalent concentration: NA.

Was a conversion used from intermittent to continuous exposure? No.

Other additional studies or pertinent information which lend support to this MRL: Similar adverse effects on testicular histology and sperm numbers occurred in adult male offspring of mice that were orally exposed to γ-HCH in doses ≥15 mg/kg/day (lower doses not tested) on gestation days 9–16 (Traina et al. 2003). Testicular and other reproductive effects occurred in intermediate-duration studies of lindane in mink at the same dose as the acute LOAEL for developmental/reproductive toxicity in rats. Female mink treated with 1 mg/kg/day γ-HCH in their diet from 3–6 weeks before mating until weaning at 8–10 weeks postpartum showed effects on reproductive efficiency that included reduced receptivity to a second mating and reduced whelping rate, although litter size was not affected (Beard et al. 1997). This decreased fertility effect was primarily a result of embryo mortality after implantation. Reductions in litter size as well as whelping rate were observed in a three-generation study of mink exposed to 1 mg/kg/day γ-HCH in the diet (Beard and Rawlings 1998). Neurological effects of γ-HCH occurred at acute doses similar to and higher than the 1 mg/kg/day LOAEL for developmental/reproductive toxicity. Neurological responses included enhanced susceptibility to kindling (induction of seizures by repeated subthreshold electrical stimulation of the brain) following a single 5-mg/kg dose (Gilbert and Mack 1995) or 3 mg/kg/day for 4 days (Joy et al. 1982), reduced brain serotonin level following 3 mg/kg/day for 6 days (Attia et al. 1991), and reduced brain barrier permeability in 10-day-old pups exposed to 2 mg/kg as a single dose or 8 daily doses (Gupta et al. 1999). The toxicological relevance of these effects is unclear because there were no concurrent tests of neurobehavioral function (as well as the unnatural method of seizure induction).

A comprehensive neurotoxicity screening study was conducted in which groups of 10 male and 10 female Crl:CD BR rats were administered a single dose of γ-HCH by gavage at levels of 0, 6, 20, or 60 mg/kg (Hughes 1999a). This study is an unpublished CBI submission summarized by EPA (2000). End points included functional observational battery (FOB) and motor activity (MA) tests performed prior to treatment, within 3 hours of dosing, and on post-exposure days 7 and 14, as well as histopathology of nervous system tissues at study termination. No clinical signs or any other effects were observed at 6 mg/kg. Motor activity was decreased in females at ≥20 mg/kg and males at 60 mg/kg. Females also had increased forelimb grip strength and decreased grooming behavior at 20 mg/kg, as well as an absence of grooming behavior at 60 mg/kg. Other effects at 60 mg/kg included clinical signs (e.g., piloerection, urine-stained fur, tremors, and/or convulsions) in both sexes and increased hindlimb foot splay in males. Other acute effects of γ-HCH included hematological and immunological changes in mice at 10–20 mg/kg/day (Hong and Boorman 1993), developmental changes in rats and mice at 20–45 mg/kg/day in rats and mice (Dalsenter et al. 1997b; Hassoun and Stohs 1996a; Rivera et al. 1991), and liver and kidney changes in mice at 72 mg/kg/day (Srinivasan and Radhakrishnamurty 1988; Srinivasan et al. 1984).

Agency Contact (Chemical Manager): Alfred Dorsey, D.V.M.

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

Chemical Name: γ-HCH
CAS Number: 58-89-9
Date: June 2005
Profile Status: Final Post-Public Comment Draft
Route: [ ] Inhalation [X] Oral
Duration: [ ] Acute [X] Intermediate [ ] Chronic
Graph Key: 45
Species: Mouse

Minimal Risk Level: 0.00001 [X] mg/kg/day [ ] ppm

Reference: Meera P, Rao PR, Shanker R, et al. 1992. Immunomodulatory effects of γ-HCH (lindane) in mice. Immunopharmacol Immunotoxicol 14:261-282.

Experimental design: Groups of six female Swiss mice were exposed to γ-HCH in measured dietary doses of 0, 0.012, 0.12, or 1.2 mg/kg/day for up to 24 weeks in an immunotoxicity study. End points that were evaluated throughout the study included delayed-type hypersensitivity reaction to sheep red blood cells (SRBC), lymphoproliferative response to mitogenic stimulation by concavalin A, mixed lymphocyte reactions, response of IgM antibody forming cells in spleen (plaque formation) to SRBC or lipopolysaccharide (LPS), and peritoneal macrophage phagocytic activity in response to LPS or *Staphylococcus aureus*. Histology of the thymus, peripheral lymph nodes, and spleen was evaluated at 4, 12, and 24 weeks post-treatment.

Effects noted in study and corresponding doses: Both cell-mediated and humoral components of the immune system showed a biphasic response, characterized initially by stimulation followed by suppression in a dose-dependent manner at all dose levels, indicating that a NOAEL was not identified. Effects observed at ≥0.012 mg/kg/day included biphasic changes in delayed-type hypersensitivity reaction to SRBC (increased at 4–12 weeks and decreased at 12–24 weeks), IgM plaque formation to SRBC (increased at 4–8 weeks and decreased at 12–24 weeks), and plaque formation to LPS-SRBC (increased at 4 weeks at ≥0.12 mg/kg/day and decreased at 8–24 weeks at ≥0.012 mg/kg/day). Histological changes occurred in lymphoid organs of treated animals and were consistent with the biphasic immunomodulatory responses. Effects were observed in the spleen at ≥0.12 mg/kg/day, including no significant reaction except for active proliferation of megakaryocytes at 4 weeks post-treatment, an apparent reduction in lymphoid follicles at 12 weeks post-treatment, and considerable reduction in the overall cellularity of red pulp and white pulp areas at 24 weeks post-treatment. Histopathology at 1.2 mg/kg/day included effects in lymph nodes (reduced lymphocyte population and size of medullary cords) and thymus (necrosis in the medulla) at 12–24 weeks post-treatment at 1.2 mg/kg/day.

Dose and end point used for MRL derivation: 0.012 mg/kg/day; reduced activity of lymphoid follicles with prominent megakaryocytes and delayed hypersensitivity to immune challenge.

[ ] NOAEL [X] LOAEL

Uncertainty Factors used in MRL derivation:

[X] 10 for use of a LOAEL
[X] 10 for extrapolation from animals to humans
[X] 10 for human variability

Was a conversion used from ppm in food or water to a mg/body weight dose? No.

If an inhalation study in animals, list the conversion factors used in determining human equivalent dose: NA.

Other additional studies or pertinent information which lend support to this MRL: Immunotoxic effects have been observed in other oral studies of γ-HCH. Immunosuppression in the form of reduced antibody responses to *Salmonella* and typhoid vaccines occurred in rats exposed to 6.25 mg/kg/day for up to 5 weeks (Dewan et al. 1980). Exposure to 10 mg/kg/day for 10 days caused residual bone marrow damage and suppressed granulocyte-macrophage progenitor cells in mice, and atrophy of the thymus was observed in mice following 40 mg/kg/day for 3 days (Hong and Boorman 1993). Serum antibody response to SRBC was suppressed in rats exposed to 3.6 mg/kg/day for 8 weeks (Koner et al. 1998).

Agency Contact (Chemical Manager): Alfred Dorsey, D.V.M.

APPENDIX B. USER'S GUIDE

Chapter 1

Public Health Statement

This chapter of the profile is a health effects summary written in non-technical language. Its intended audience is the general public, especially people living in the vicinity of a hazardous waste site or chemical release. If the Public Health Statement were removed from the rest of the document, it would still communicate to the lay public essential information about the chemical.

The major headings in the Public Health Statement are useful to find specific topics of concern. The topics are written in a question and answer format. The answer to each question includes a sentence that will direct the reader to chapters in the profile that will provide more information on the given topic.

Chapter 2

Relevance to Public Health

This chapter provides a health effects summary based on evaluations of existing toxicologic, epidemiologic, and toxicokinetic information. This summary is designed to present interpretive, weight-of-evidence discussions for human health end points by addressing the following questions:

1. What effects are known to occur in humans?

2. What effects observed in animals are likely to be of concern to humans?

3. What exposure conditions are likely to be of concern to humans, especially around hazardous waste sites?

The chapter covers end points in the same order that they appear within the Discussion of Health Effects by Route of Exposure section, by route (inhalation, oral, and dermal) and within route by effect. Human data are presented first, then animal data. Both are organized by duration (acute, intermediate, chronic). *In vitro* data and data from parenteral routes (intramuscular, intravenous, subcutaneous, etc.) are also considered in this chapter.

The carcinogenic potential of the profiled substance is qualitatively evaluated, when appropriate, using existing toxicokinetic, genotoxic, and carcinogenic data. ATSDR does not currently assess cancer potency or perform cancer risk assessments. Minimal Risk Levels (MRLs) for noncancer end points (if derived) and the end points from which they were derived are indicated and discussed.

Limitations to existing scientific literature that prevent a satisfactory evaluation of the relevance to public health are identified in the Chapter 3 Data Needs section.

Interpretation of Minimal Risk Levels

Where sufficient toxicologic information is available, ATSDR has derived MRLs for inhalation and oral routes of entry at each duration of exposure (acute, intermediate, and chronic). These MRLs are not meant to support regulatory action, but to acquaint health professionals with exposure levels at which adverse health effects are not expected to occur in humans.

MRLs should help physicians and public health officials determine the safety of a community living near a chemical emission, given the concentration of a contaminant in air or the estimated daily dose in water. MRLs are based largely on toxicological studies in animals and on reports of human occupational exposure.

MRL users should be familiar with the toxicologic information on which the number is based. Chapter 2, "Relevance to Public Health," contains basic information known about the substance. Other sections such as Chapter 3 Section 3.9, "Interactions with Other Substances," and Section 3.10, "Populations that are Unusually Susceptible" provide important supplemental information.

MRL users should also understand the MRL derivation methodology. MRLs are derived using a modified version of the risk assessment methodology that the Environmental Protection Agency (EPA) provides (Barnes and Dourson 1988) to determine reference doses (RfDs) for lifetime exposure.

To derive an MRL, ATSDR generally selects the most sensitive end point which, in its best judgement, represents the most sensitive human health effect for a given exposure route and duration. ATSDR cannot make this judgement or derive an MRL unless information (quantitative or qualitative) is available for all potential systemic, neurological, and developmental effects. If this information and reliable quantitative data on the chosen end point are available, ATSDR derives an MRL using the most sensitive species (when information from multiple species is available) with the highest no-observed-adverse-effect level (NOAEL) that does not exceed any adverse effect levels. When a NOAEL is not available, a lowest-observed-adverse-effect level (LOAEL) can be used to derive an MRL, and an uncertainty factor (UF) of 10 must be employed. Additional uncertainty factors of 10 must be used both for human variability to protect sensitive subpopulations (people who are most susceptible to the health effects caused by the substance) and for interspecies variability (extrapolation from animals to humans). In deriving an MRL, these individual uncertainty factors are multiplied together. The product is then divided into the inhalation concentration or oral dosage selected from the study. Uncertainty factors used in developing a substance-specific MRL are provided in the footnotes of the levels of significant exposure (LSE) tables.

Chapter 3

Health Effects

Tables and Figures for Levels of Significant Exposure (LSE)

Tables and figures are used to summarize health effects and illustrate graphically levels of exposure associated with those effects. These levels cover health effects observed at increasing dose concentrations and durations, differences in response by species, MRLs to humans for noncancer end points, and EPA's estimated range associated with an upper- bound individual lifetime cancer risk of 1 in 10,000 to 1 in 10,000,000. Use the LSE tables and figures for a quick review of the health effects and to locate data for a specific exposure scenario. The LSE tables and figures should always be used in conjunction with the text. All entries in these tables and figures represent studies that provide reliable, quantitative estimates of NOAELs, LOAELs, or Cancer Effect Levels (CELs).

The legends presented below demonstrate the application of these tables and figures. Representative examples of LSE Table 3-1 and Figure 3-1 are shown. The numbers in the left column of the legends correspond to the numbers in the example table and figure.

LEGEND

See Sample LSE Table 3-1 (page B-6)

(1) Route of Exposure. One of the first considerations when reviewing the toxicity of a substance using these tables and figures should be the relevant and appropriate route of exposure. Typically when sufficient data exist, three LSE tables and two LSE figures are presented in the document. The three LSE tables present data on the three principal routes of exposure, i.e., inhalation, oral, and dermal (LSE Tables 3-1, 3-2, and 3-3, respectively). LSE figures are limited to the inhalation (LSE Figure 3-1) and oral (LSE Figure 3-2) routes. Not all substances will have data on each route of exposure and will not, therefore, have all five of the tables and figures.

(2) Exposure Period. Three exposure periods—acute (less than 15 days), intermediate (15–364 days), and chronic (365 days or more)—are presented within each relevant route of exposure. In this example, an inhalation study of intermediate exposure duration is reported. For quick reference to health effects occurring from a known length of exposure, locate the applicable exposure period within the LSE table and figure.

(3) Health Effect. The major categories of health effects included in LSE tables and figures are death, systemic, immunological, neurological, developmental, reproductive, and cancer. NOAELs and LOAELs can be reported in the tables and figures for all effects but cancer. Systemic effects are further defined in the "System" column of the LSE table (see key number 18).

(4) Key to Figure. Each key number in the LSE table links study information to one or more data points using the same key number in the corresponding LSE figure. In this example, the study represented by key number 18 has been used to derive a NOAEL and a Less Serious LOAEL (also see the two "18r" data points in sample Figure 3-1).

(5) Species. The test species, whether animal or human, are identified in this column. Chapter 2, "Relevance to Public Health," covers the relevance of animal data to human toxicity and Section 3.4, "Toxicokinetics," contains any available information on comparative toxicokinetics. Although NOAELs and LOAELs are species specific, the levels are extrapolated to equivalent human doses to derive an MRL.

(6) Exposure Frequency/Duration. The duration of the study and the weekly and daily exposure regimens are provided in this column. This permits comparison of NOAELs and LOAELs from different studies. In this case (key number 18), rats were exposed to “Chemical x” via inhalation for 6 hours/day, 5 days/week, for 13 weeks. For a more complete review of the dosing regimen, refer to the appropriate sections of the text or the original reference paper (i.e., Nitschke et al. 1981).

(7) System. This column further defines the systemic effects. These systems include respiratory, cardiovascular, gastrointestinal, hematological, musculoskeletal, hepatic, renal, and dermal/ocular. "Other" refers to any systemic effect (e.g., a decrease in body weight) not covered in these systems. In the example of key number 18, one systemic effect (respiratory) was investigated.

(8) NOAEL. A NOAEL is the highest exposure level at which no harmful effects were seen in the organ system studied. Key number 18 reports a NOAEL of 3 ppm for the respiratory system, which was used to derive an intermediate exposure, inhalation MRL of 0.005 ppm (see footnote "b").

(9) LOAEL. A LOAEL is the lowest dose used in the study that caused a harmful health effect. LOAELs have been classified into "Less Serious" and "Serious" effects. These distinctions help readers identify the levels of exposure at which adverse health effects first appear and the gradation of effects with increasing dose. A brief description of the specific end point used to quantify the adverse effect accompanies the LOAEL. The respiratory effect reported in key number 18 (hyperplasia) is a Less Serious LOAEL of 10 ppm. MRLs are not derived from Serious LOAELs.

(10) Reference. The complete reference citation is given in Chapter 9 of the profile.

(11) CEL. A CEL is the lowest exposure level associated with the onset of carcinogenesis in experimental or epidemiologic studies. CELs are always considered serious effects. The LSE tables and figures do not contain NOAELs for cancer, but the text may report doses not causing measurable cancer increases.

(12) Footnotes. Explanations of abbreviations or reference notes for data in the LSE tables are found in the footnotes. Footnote "b" indicates that the NOAEL of 3 ppm in key number 18 was used to derive an MRL of 0.005 ppm.

LEGEND

See Sample Figure 3-1 (page B-7)

LSE figures graphically illustrate the data presented in the corresponding LSE tables. Figures help the reader quickly compare health effects according to exposure concentrations for particular exposure periods.

(13) Exposure Period. The same exposure periods appear as in the LSE table. In this example, health effects observed within the acute and intermediate exposure periods are illustrated.

(14) Health Effect. These are the categories of health effects for which reliable quantitative data exists. The same health effects appear in the LSE table.

(15) Levels of Exposure. Concentrations or doses for each health effect in the LSE tables are graphically displayed in the LSE figures. Exposure concentration or dose is measured on the log scale "y" axis. Inhalation exposure is reported in mg/m^3 or ppm and oral exposure is reported in mg/kg/day.

(16) NOAEL. In this example, the open circle designated 18r identifies a NOAEL critical end point in the rat upon which an intermediate inhalation exposure MRL is based. The key number 18 corresponds to the entry in the LSE table. The dashed descending arrow indicates the extrapolation from the exposure level of 3 ppm (see entry 18 in the table) to the MRL of 0.005 ppm (see footnote "b" in the LSE table).

(17) CEL. Key number 38m is one of three studies for which CELs were derived. The diamond symbol refers to a CEL for the test species-mouse. The number 38 corresponds to the entry in the LSE table.

(18) Estimated Upper-Bound Human Cancer Risk Levels. This is the range associated with the upper-bound for lifetime cancer risk of 1 in 10,000 to 1 in 10,000,000. These risk levels are derived from the EPA's Human Health Assessment Group's upper-bound estimates of the slope of the cancer dose response curve at low dose levels (q_1*).

(19) Key to LSE Figure. The Key explains the abbreviations and symbols used in the figure.

SAMPLE

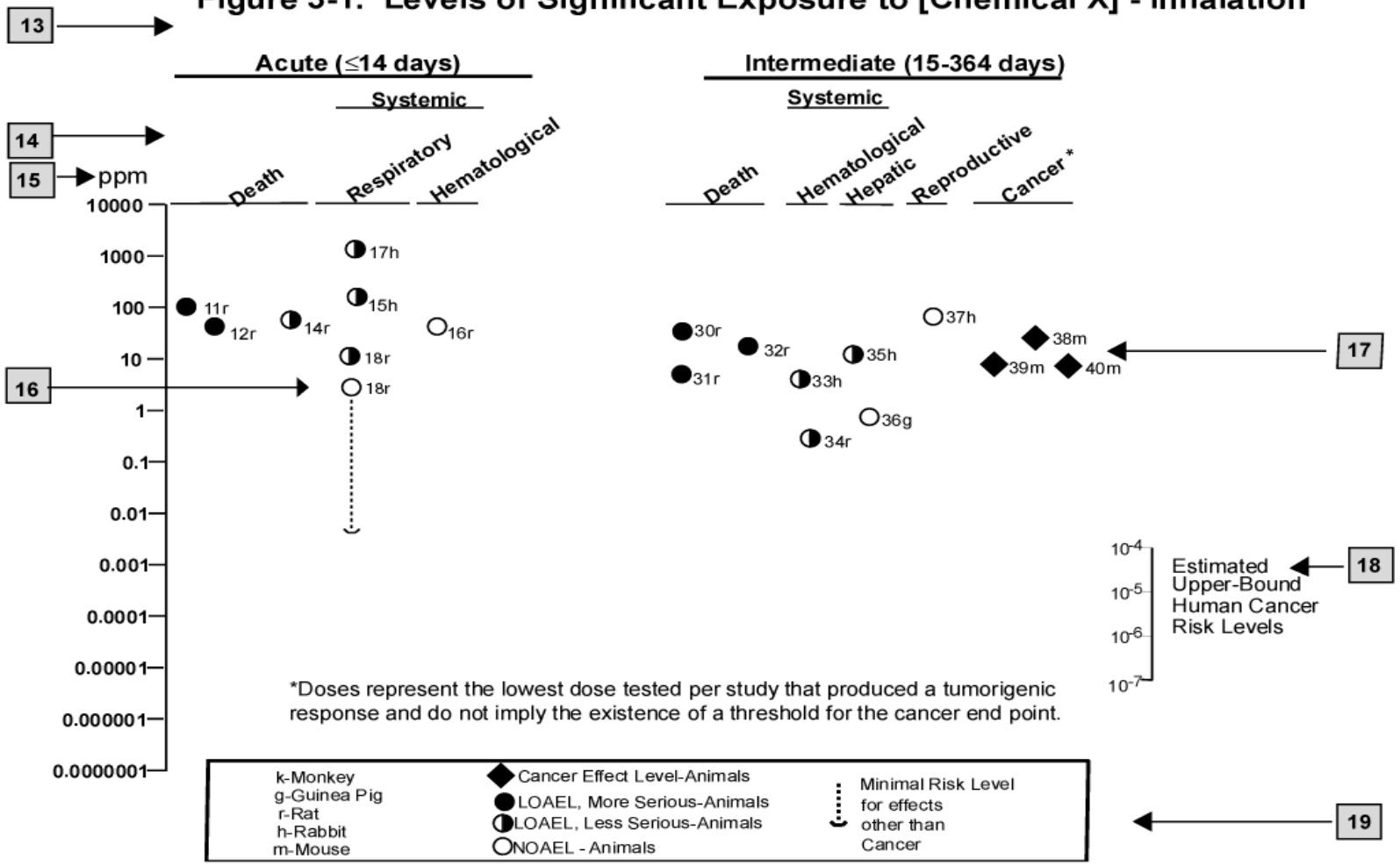
1 → **Table 3-1. Levels of Significant Exposure to [Chemical x] – Inhalation**

Key to figure[a]	Species	Exposure frequency/ duration	System	NOAEL (ppm)	LOAEL (effect) Less serious (ppm)	Serious (ppm)	Reference
2 → INTERMEDIATE EXPOSURE							
	5	6	7	8	9		10
3 → Systemic	↓	↓	↓	↓	↓		↓
18	Rat	13 wk 5 d/wk 6 hr/d	Resp	3[b]	10 (hyperplasia)		Nitschke et al. 1981
4 → CHRONIC EXPOSURE							
Cancer					11		
					↓		
38	Rat	18 mo 5 d/wk 7 hr/d			20	(CEL, multiple organs)	Wong et al. 1982
39	Rat	89–104 wk 5 d/wk 6 hr/d			10	(CEL, lung tumors, nasal tumors)	NTP 1982
40	Mouse	79–103 wk 5 d/wk 6 hr/d			10	(CEL, lung tumors, hemangiosarcomas)	NTP 1982

12 → [a] The number corresponds to entries in Figure 3-1.
[b] Used to derive an intermediate inhalation Minimal Risk Level (MRL) of $5x10^{-3}$ ppm; dose adjusted for intermittent exposure and divided by an uncertainty factor of 100 (10 for extrapolation from animal to humans, 10 for human variability).

SAMPLE

Figure 3-1. Levels of Significant Exposure to [Chemical X] - Inhalation



APPENDIX C. ACRONYMS, ABBREVIATIONS, AND SYMBOLS

ACGIH	American Conference of Governmental Industrial Hygienists
ACOEM	American College of Occupational and Environmental Medicine
ADI	acceptable daily intake
ADME	absorption, distribution, metabolism, and excretion
AED	atomic emission detection
AFID	alkali flame ionization detector
AFOSH	Air Force Office of Safety and Health
ALT	alanine aminotransferase
AML	acute myeloid leukemia
AOAC	Association of Official Analytical Chemists
AOEC	Association of Occupational and Environmental Clinics
AP	alkaline phosphatase
APHA	American Public Health Association
AST	aspartate aminotransferase
atm	atmosphere
ATSDR	Agency for Toxic Substances and Disease Registry
AWQC	Ambient Water Quality Criteria
BAT	best available technology
BCF	bioconcentration factor
BEI	Biological Exposure Index
BMD	benchmark dose
BMR	benchmark response
BSC	Board of Scientific Counselors
C	centigrade
CAA	Clean Air Act
CAG	Cancer Assessment Group of the U.S. Environmental Protection Agency
CAS	Chemical Abstract Services
CDC	Centers for Disease Control and Prevention
CEL	cancer effect level
CELDS	Computer-Environmental Legislative Data System
CERCLA	Comprehensive Environmental Response, Compensation, and Liability Act
CFR	Code of Federal Regulations
Ci	curie
CI	confidence interval
CL	ceiling limit value
CLP	Contract Laboratory Program
cm	centimeter
CML	chronic myeloid leukemia
CPSC	Consumer Products Safety Commission
CWA	Clean Water Act
DHEW	Department of Health, Education, and Welfare
DHHS	Department of Health and Human Services
DNA	deoxyribonucleic acid
DOD	Department of Defense
DOE	Department of Energy
DOL	Department of Labor
DOT	Department of Transportation

APPENDIX C

DOT/UN/ NA/IMCO	Department of Transportation/United Nations/ North America/International Maritime Dangerous Goods Code
DWEL	drinking water exposure level
ECD	electron capture detection
ECG/EKG	electrocardiogram
EEG	electroencephalogram
EEGL	Emergency Exposure Guidance Level
EPA	Environmental Protection Agency
F	Fahrenheit
F_1	first-filial generation
FAO	Food and Agricultural Organization of the United Nations
FDA	Food and Drug Administration
FEMA	Federal Emergency Management Agency
FIFRA	Federal Insecticide, Fungicide, and Rodenticide Act
FPD	flame photometric detection
fpm	feet per minute
FR	Federal Register
FSH	follicle stimulating hormone
g	gram
GC	gas chromatography
gd	gestational day
GLC	gas liquid chromatography
GPC	gel permeation chromatography
HPLC	high-performance liquid chromatography
HRGC	high resolution gas chromatography
HSDB	Hazardous Substance Data Bank
IARC	International Agency for Research on Cancer
IDLH	immediately dangerous to life and health
ILO	International Labor Organization
IRIS	Integrated Risk Information System
Kd	adsorption ratio
kg	kilogram
kkg	metric ton
K_{oc}	organic carbon partition coefficient
K_{ow}	octanol-water partition coefficient
L	liter
LC	liquid chromatography
LC_{50}	lethal concentration, 50% kill
LC_{Lo}	lethal concentration, low
LD_{50}	lethal dose, 50% kill
LD_{Lo}	lethal dose, low
LDH	lactic dehydrogenase
LH	luteinizing hormone
LOAEL	lowest-observed-adverse-effect level
LSE	Levels of Significant Exposure
LT_{50}	lethal time, 50% kill
m	meter
MA	*trans*,*trans*-muconic acid
MAL	maximum allowable level
mCi	millicurie
MCL	maximum contaminant level

MCLG	maximum contaminant level goal
MF	modifying factor
MFO	mixed function oxidase
mg	milligram
mL	milliliter
mm	millimeter
mmHg	millimeters of mercury
mmol	millimole
mppcf	millions of particles per cubic foot
MRL	Minimal Risk Level
MS	mass spectrometry
NAAQS	National Ambient Air Quality Standard
NAS	National Academy of Science
NATICH	National Air Toxics Information Clearinghouse
NATO	North Atlantic Treaty Organization
NCE	normochromatic erythrocytes
NCEH	National Center for Environmental Health
NCI	National Cancer Institute
ND	not detected
NFPA	National Fire Protection Association
ng	nanogram
NHANES	National Health and Nutrition Examination Survey
NIEHS	National Institute of Environmental Health Sciences
NIOSH	National Institute for Occupational Safety and Health
NIOSHTIC	NIOSH's Computerized Information Retrieval System
NLM	National Library of Medicine
nm	nanometer
nmol	nanomole
NOAEL	no-observed-adverse-effect level
NOES	National Occupational Exposure Survey
NOHS	National Occupational Hazard Survey
NPD	nitrogen phosphorus detection
NPDES	National Pollutant Discharge Elimination System
NPL	National Priorities List
NR	not reported
NRC	National Research Council
NS	not specified
NSPS	New Source Performance Standards
NTIS	National Technical Information Service
NTP	National Toxicology Program
ODW	Office of Drinking Water, EPA
OERR	Office of Emergency and Remedial Response, EPA
OHM/TADS	Oil and Hazardous Materials/Technical Assistance Data System
OPP	Office of Pesticide Programs, EPA
OPPT	Office of Pollution Prevention and Toxics, EPA
OPPTS	Office of Prevention, Pesticides and Toxic Substances, EPA
OR	odds ratio
OSHA	Occupational Safety and Health Administration
OSW	Office of Solid Waste, EPA
OTS	Office of Toxic Substances
OW	Office of Water

OWRS	Office of Water Regulations and Standards, EPA
PAH	polycyclic aromatic hydrocarbon
PBPD	physiologically based pharmacodynamic
PBPK	physiologically based pharmacokinetic
PCE	polychromatic erythrocytes
PEL	permissible exposure limit
pg	picogram
PHS	Public Health Service
PID	photo ionization detector
pmol	picomole
PMR	proportionate mortality ratio
ppb	parts per billion
ppm	parts per million
ppt	parts per trillion
PSNS	pretreatment standards for new sources
RBC	red blood cell
REL	recommended exposure level/limit
RfC	reference concentration
RfD	reference dose
RNA	ribonucleic acid
RQ	reportable quantity
RTECS	Registry of Toxic Effects of Chemical Substances
SARA	Superfund Amendments and Reauthorization Act
SCE	sister chromatid exchange
SGOT	serum glutamic oxaloacetic transaminase
SGPT	serum glutamic pyruvic transaminase
SIC	standard industrial classification
SIM	selected ion monitoring
SMCL	secondary maximum contaminant level
SMR	standardized mortality ratio
SNARL	suggested no adverse response level
SPEGL	Short-Term Public Emergency Guidance Level
STEL	short term exposure limit
STORET	Storage and Retrieval
TD_{50}	toxic dose, 50% specific toxic effect
TLV	threshold limit value
TOC	total organic carbon
TPQ	threshold planning quantity
TRI	Toxics Release Inventory
TSCA	Toxic Substances Control Act
TWA	time-weighted average
UF	uncertainty factor
U.S.	United States
USDA	United States Department of Agriculture
USGS	United States Geological Survey
VOC	volatile organic compound
WBC	white blood cell
WHO	World Health Organization

>	greater than
≥	greater than or equal to
=	equal to
<	less than
≤	less than or equal to
%	percent
α	alpha
β	beta
γ	gamma
δ	delta
µm	micrometer
µg	microgram
q_1^*	cancer slope factor
–	negative
+	positive
(+)	weakly positive result
(–)	weakly negative result

APPENDIX D. INDEX