CHAPTER 2. HEALTH EFFECTS

2.1 INTRODUCTION

The primary purpose of this chapter is to provide public health officials, physicians, toxicologists, and other interested individuals and groups with an overall perspective on the toxicology of BCEE. It contains descriptions and evaluations of toxicological studies and epidemiological investigations and provides conclusions, where possible, on the relevance of toxicity and toxicokinetic data to public health. When available, mechanisms of action are discussed along with the health effects data; toxicokinetic mechanistic data are discussed in Section 3.1.

A glossary and list of acronyms, abbreviations, and symbols can be found at the end of this profile.

To help public health professionals and others address the needs of persons living or working near hazardous waste sites, the information in this section is organized by health effect. These data are discussed in terms of route of exposure (inhalation, oral, and dermal) and three exposure periods: acute (≤14 days), intermediate (15–364 days), and chronic (≥365 days).

As discussed in Appendix B, a literature search was conducted to identify relevant studies examining health effect endpoints. Figure 2-1 provides an overview of the database of studies in humans or experimental animals included in this chapter of the profile. These studies evaluate the potential health effects associated with inhalation, oral, or dermal exposure to BCEE, but may not be inclusive of the entire body of literature.

Levels of significant exposure (LSEs) for each route and duration are presented in tables and illustrated in figures. Animal inhalation studies are presented in Table 2-1 and Figure 2-2, animal oral studies are presented in Table 2-2 and Figure 2-3, and animal dermal studies are presented in Table 2-3.

The points in the figures showing no-observed-adverse-effect levels (NOAELs) or lowest-observed-adverse-effect levels (LOAELs) reflect the actual doses (levels of exposure) used in the studies. LOAELs have been classified into "less serious" or "serious" effects. "Serious" effects are those that evoke failure in a biological system and can lead to morbidity or mortality (e.g., acute respiratory distress or death). "Less serious" effects are those that are not expected to cause significant dysfunction or death, or those whose significance to the organism is not entirely clear. ATSDR acknowledges that a considerable amount of judgment may be required in establishing whether an endpoint should be classified as a NOAEL, "less serious" LOAEL, or "serious" LOAEL, and that in some cases, there will be insufficient

data to decide whether the effect is indicative of significant dysfunction. However, the Agency has established guidelines and policies that are used to classify these endpoints. ATSDR believes that there is sufficient merit in this approach to warrant an attempt at distinguishing between "less serious" and "serious" effects. The distinction between "less serious" effects and "serious" effects is considered to be important because it helps the users of the profiles to identify levels of exposure at which major health effects start to appear. LOAELs or NOAELs should also help in determining whether or not the effects vary with dose and/or duration, and place into perspective the possible significance of these effects to human health. Levels of exposure associated with cancer (Cancer Effect Levels, CELs) of BCEE are indicated in Table 2-2 and Figure 2-3.

A User's Guide has been provided at the end of this profile (see Appendix C). This guide should aid in the interpretation of the tables and figures for LSEs and MRLs.

The health effects of BCEE have been evaluated in a human experimental study and in animal studies. As illustrated in Figure 2-1, most of the health effects data come from inhalation studies in animals. In addition to the studies summarized in Figure 2-1, seven studies have examined the acute lethality of BCEE following inhalation, oral, or dermal exposure. Animal data are available for most health effect category, but these data are mostly derived from a single intermediate-duration inhalation study that identified NOAEL values for most effects. It is noted that no studies examined reproductive function, immune function, or developmental toxicity.

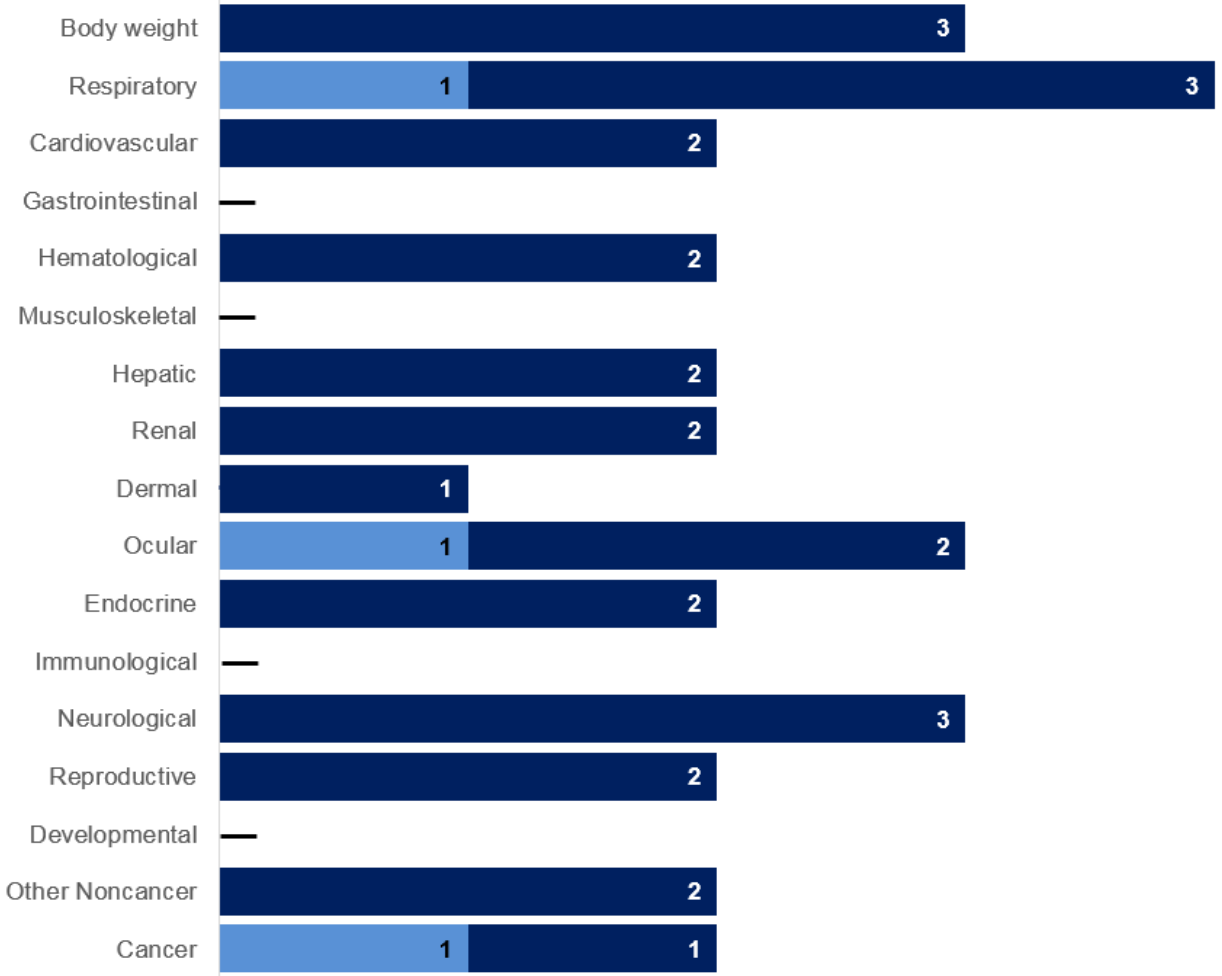
The available human and animal studies suggest the following sensitive targets of toxicity:

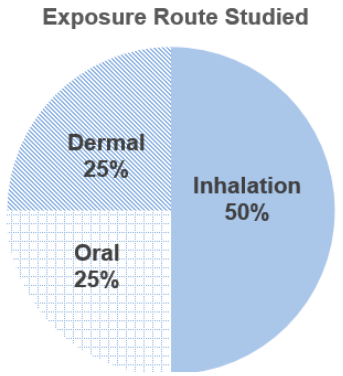
- **Respiratory Endpoint:** Nasal irritation has been reported by humans briefly exposed to BCEE and has been noted in laboratory animals. At higher, lethal concentrations of airborne BCEE, lung congestion and edema have been observed.
- **Ocular Endpoint:** Ocular irritation has been observed in laboratory animals exposed to airborne BCEE and following direct instillation.
- **Nervous System Endpoint:** At lethal concentrations, loss of consciousness and decreased motility have been observed in laboratory animals.
- **Body Weight Endpoint:** Decreases in body weight gain have been observed following intermediate-duration inhalation exposure and chronic-duration oral exposure.

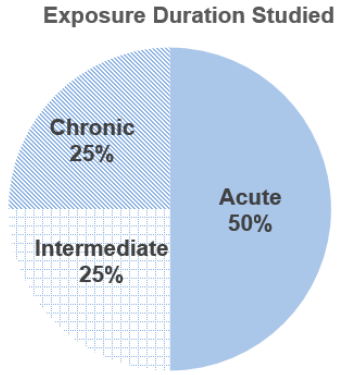
Figure 2-1. Overview of the Number of Studies Examining Bis(2-Chloroethyl)Ether Health Effects

Most studies examined the potential body weight, respiratory, and nervous system effects of bis(2-chloroethyl)ether

More studies evaluated health effects in **animals** than **humans** (counts represent studies examining endpoint)







*Includes studies discussed in Chapter 2. A total of 7 studies (including those finding no effect) have examined toxicity; most studies examined multiple endpoints.

Table 2-1. Levels of Significant Exposure to Bis(2-Chloroethyl)Ether – Inhalation

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (ppm)	Parameters monitored	Endpoint	NOAEL (ppm)	Less serious LOAEL (ppm)	Serious LOAEL (ppm)	Effect
ACUTE EXPOSURE									
1	Rat 6 M,F	4 hours	175–340	LE	Death			250	Death in 2, 3, or 4 of 6 rats
Carpenter et al. 1949									
2	Guinea pigs 6	1–15 hours	0, 35, 105, 260, 550, 1,000	CS, GN, HP	Death			105	Deaths occurred with 5–7 hours at 1,000 ppm, 8–12 hours at 260 ppm, and after 13 hours at 105 ppm
					Respiratory		35	105	Slight nasal irritation at 35 ppm, lung congestion, edema, and hemorrhage at ≥105 ppm
					Ocular	35	105		Squinting at ≥105 ppm, lacrimation at ≥260 ppm
					Neurological	35		105	Unconsciousness, decreased motility
Schrenk et al. 1933									
3	Rat 6	45 minutes	1,000	LE	Death			1,000	3/6 animals died
Smyth and Carpenter 1948									
INTERMEDIATE EXPOSURE									
4	Rat 15 M,F	7 hours/day 5 days/week 130 days	0, 69	BW, OW, GN, HP, BC, CS, UR	Death				No deaths occurred
					Bd wt		69[b]		Decreased body weight gain
					Respiratory	69			
					Cardio	69			
					Hemato	69			
					Hepatic	69			
					Renal	69			
					Neuro	69			No effect on “behavior”
					Repro	69			No histological alterations in testes
Dow Chemical 1958									

Table 2-1. Levels of Significant Exposure to Bis(2-Chloroethyl)Ether – Inhalation

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (ppm)	Parameters monitored	Endpoint	NOAEL (ppm)	Less serious LOAEL (ppm)	Serious LOAEL (ppm)	Effect
5	Guinea pig 8 M,F	7 hours/day 5 days/week 130 days	0, 69	BW, OW, GN, HP, BC, CS, UR	Death				No deaths occurred
					Bd wt		69[b]		Decreased body weight gain
					Respiratory	69			
					Cardio	69			
					Hemato	69			
					Hepatic	69			
					Renal	69			
					Neuro	69			No effect on “behavior”
					Repro	69			No histological alterations in testes

Dow Chemical 1958

[a]The number corresponds to entries in Figure 2-2.
[b]Used to derive an intermediate-duration MRL of 0.02 ppm. Concentration adjusted for intermittent exposure, converted to an equivalent concentration in humans, and divided by an uncertainty factor of 1,000 (10 for use of a LOAEL, 10 for animal to human extrapolation, and 10 for human variability).

BC = biochemistry; BW or Bd wt = body weight; Cardio = cardiovascular; CS = clinical signs; F = female(s); GN = gross necropsy; Hemato = hematological; HP = histopathology; LE = lethality; LOAEL = lowest-observed-adverse-effect level; M = male(s); NOAEL = no-observed-adverse-effect level; Neuro = neurological; OW = organ weight; Repro = reproductive; UR = urinalysis

Figure 2-2. Levels of Significant Exposure to BCEE – Inhalation
Acute (≤ 14 days)

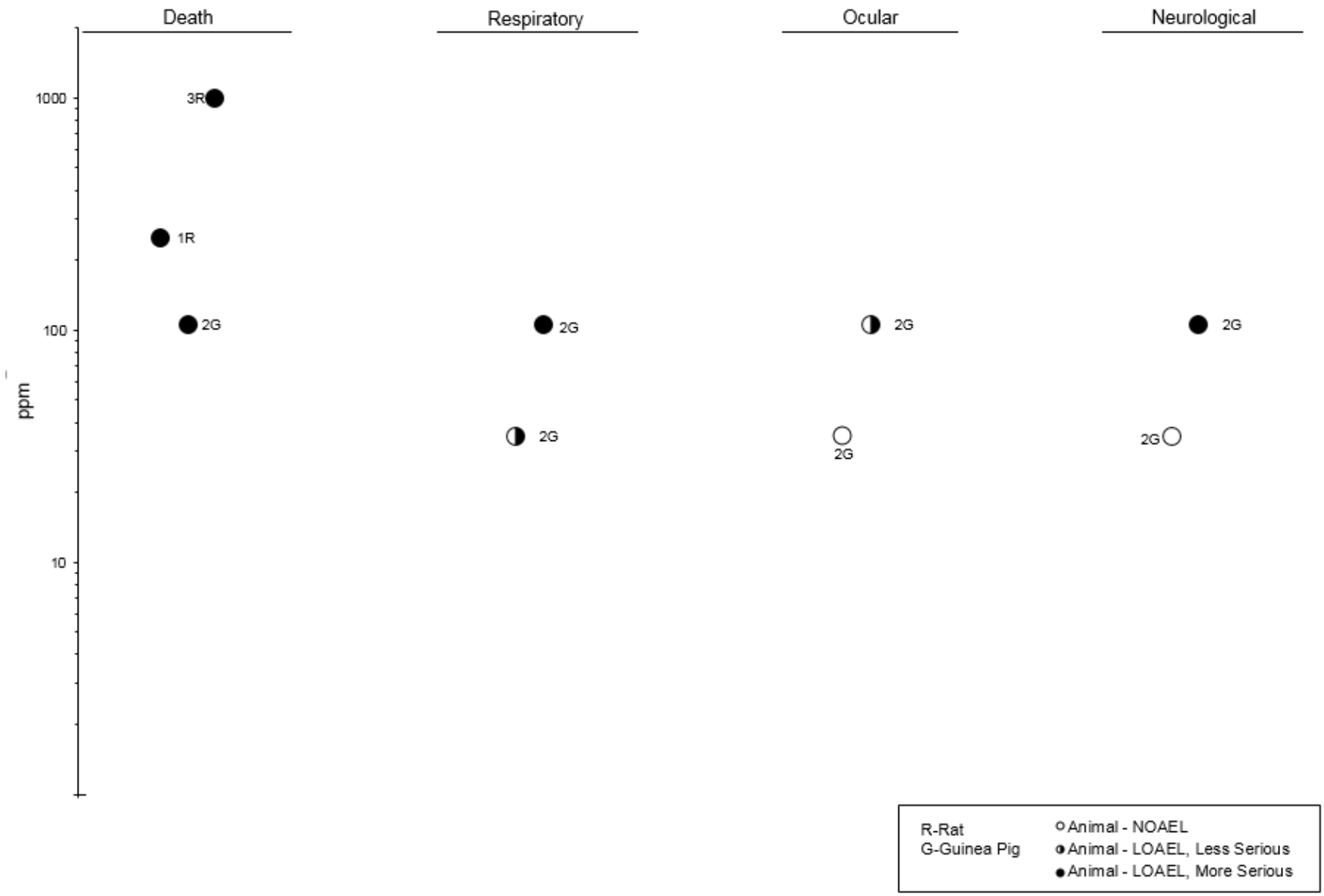


Figure 2-2. Levels of Significant Exposure to BCEE – Inhalation
Intermediate (15-364 days)

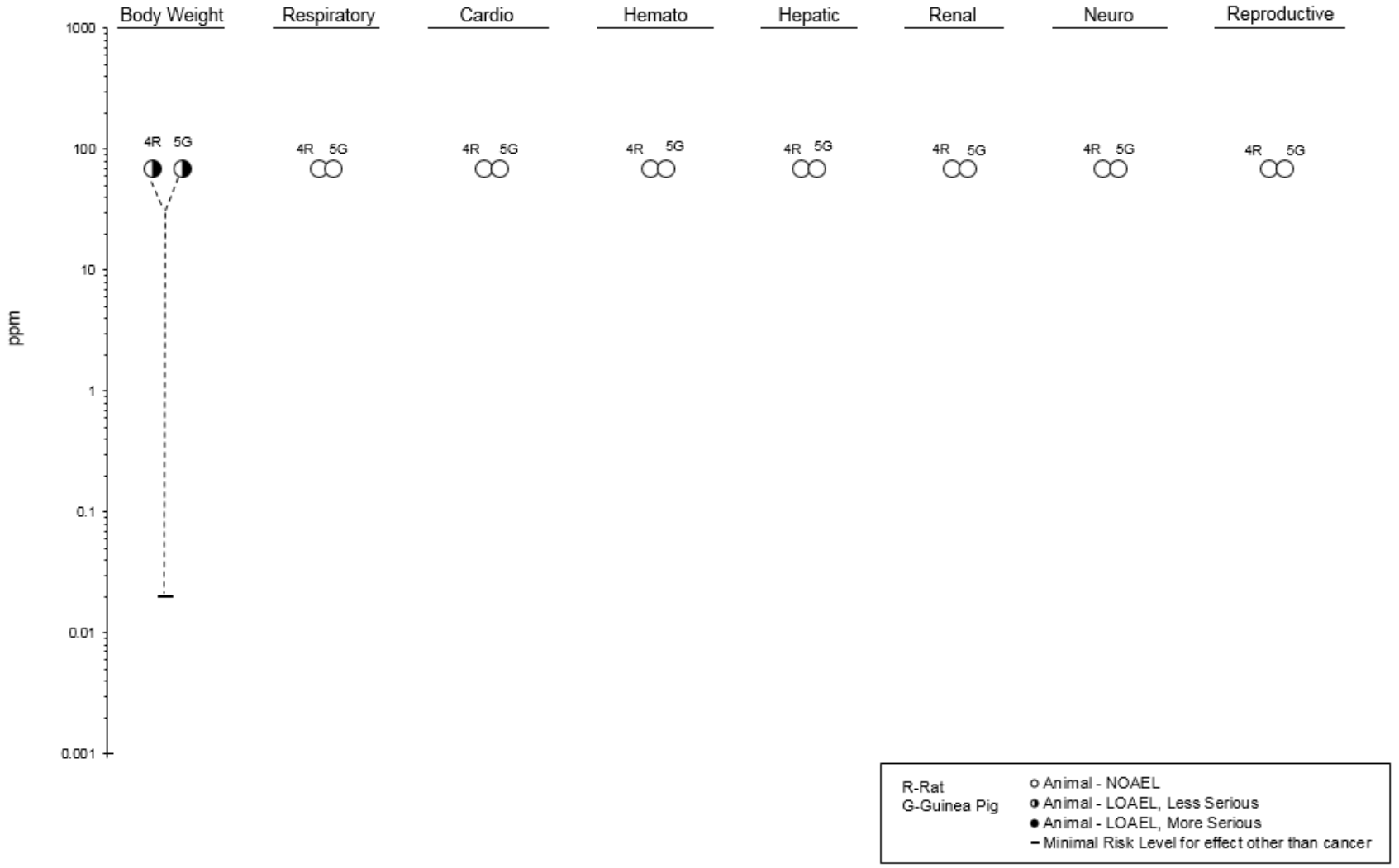


Table 2-2. Levels of Significant Exposure to Bis(2-Chloroethyl)Ether – Oral

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (mg/kg/d)	Parameters monitored	Endpoint	NOAEL (mg/kg/day)	Less serious LOAEL (mg/kg/day)	Serious LOAEL (mg/kg/day)	Effect
ACUTE EXPOSURE									
1	Rat (Sprague-Dawley) 5 M,F	Once (GO)	70, 100, 150, 210	LE, CS	Death			144	Combined LD_{50}; LD_{50} females = 122 mg/kg; LD_{50} in males= 215 mg/kg
Drake and Myer 1992									
2	Mouse (CD-1) 5 M,F	Once (GO)	140, 200, 240 290	LE, CS	Death			211	Combined LD_{50}; LD_{50} females = 209 mg/kg; LD_{50} in males= 175 mg/kg
Drake and Myer 1992									
3	Rat 6	Once (G)	NR	LE	Death			75	LD_{50}
Smyth and Carpenter 1948									
CHRONIC EXPOSURE									
4	Rat 26 M,F	2 times/week 18 months with 6-month recovery (G)	0, 25, 50	BW, GN, HP	Death			5 0F	Increased mortality at 52 weeks in females only
					Bd wt		25		Decreased body weight in females at ≥25 mg/kg and in males at 50 mg/kg
					Cancer				No increases in neoplastic lesions
Weisburger et al. 1981									
5	Mouse 18 M,F	18 months (F)	0, 41	GN, HP	Cancer			41	Increased incidence of hepatomas
Innes et al. 1969									

[a]The number corresponds to entries in Figure 2-3.

BW or Bd wt = body weight; F = female(s); (F) = exposure in feed; (G) = gavage; GN = gross necropsy; (GO) = gavage in oil vehicle; HP = histopathology; LD_{50} = lethal dose, 50% mortality; LE = lethality; LOAEL = lowest-observed-adverse-effect level; M = male(s); NOAEL = no-observed-adverse-effect level; NR = not reported

Figure 2-3. Levels of Significant Exposure to BCEE - Oral
Acute (≤ 14 days)

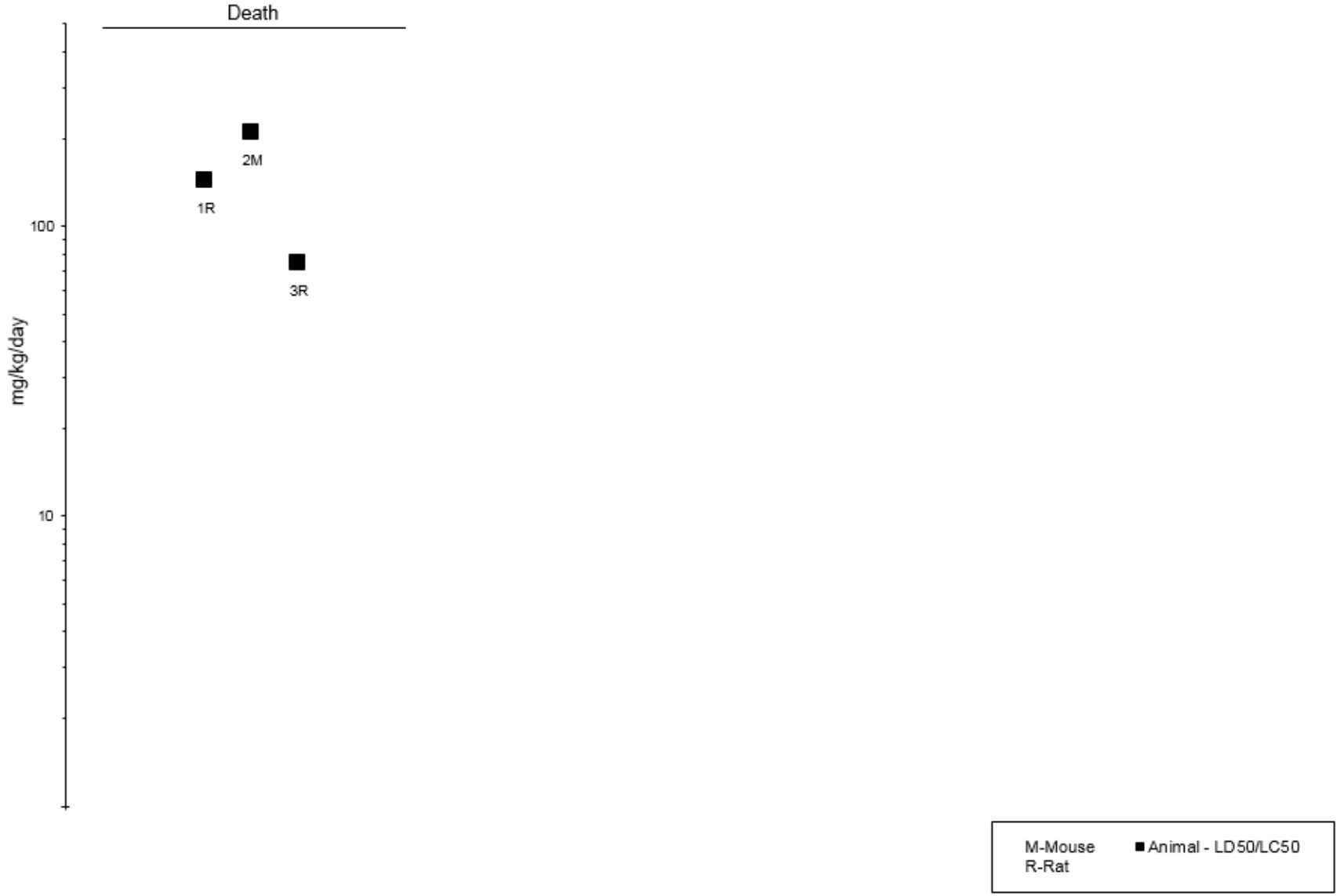


Figure 2-3. Levels of Significant Exposure to BCEE – Oral
Chronic (≥ 365 days)

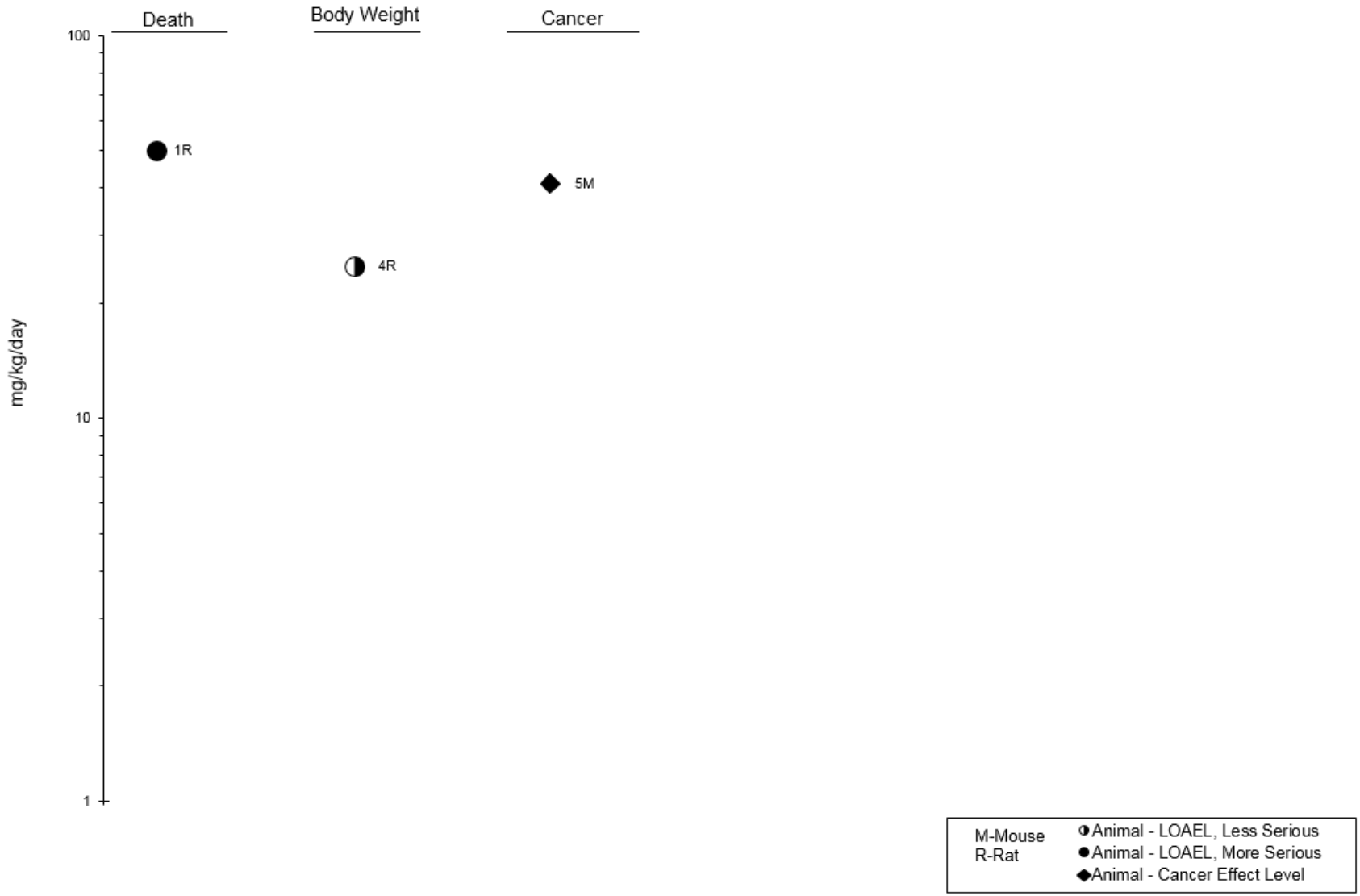


Table 2-3. Levels of Significant Exposure to Bis(2-Chloroethyl)Ether – Dermal

Species (strain) No./group	Exposure parameters	Doses	Parameters monitored	Endpoint	NOAEL	Less serious LOAEL	Serious LOAEL	Effect
ACUTE EXPOSURE								
Rabbit NR	Once	25 mg		Ocular		25 mg		Eye irritation; grade of 4 (on a scale of 1 to 10)
Carpenter and Smyth 1946								
Rabbit NR	Once	10 mg		Dermal		10 mg		Skin irritation
Smyth and Carpenter 1948								
Guinea pig 6	24 hours	366 mg/cm^2		Death			366 mg/cm^2	LD_{50}
Smyth and Carpenter 1948								
Rabbit NR	NR	NR		Death			870 mg/kg	LD_{50}
Union Carbide 1948								

LD_{50} = lethal dose, 50% mortality; LOAEL = lowest-observed-adverse-effect level; NOAEL = no-observed-adverse-effect level; NR = not reported

2.2 DEATH

There are limited data on the lethality of BCEE in humans. Elkins (1959) reported a case of death occurring in an individual exposure to BCEE vapors at a fulling mill.

In animals, acute inhalation lethality depends on the level and duration of exposure to BCEE. Exposure of animals (rats, mice guinea pigs, rabbits) to concentrations of 500–1,000 ppm caused death within 1–2 hours (Schrenk et al. 1933; Smyth and Carpenter 1948; Union Carbide 1948). Exposure of rats to 250 ppm for 4 hours caused death in about half the animals (Carpenter et al. 1949), while exposure of mice, rats, and rabbits to 200 ppm for 1 hour did not cause any deaths (Union Carbide 1948). Four of six guinea pigs exposed to 105 ppm for 13 hours died within 4 hours after the exposure, while no deaths occurred in animals exposed to 35 ppm for 13.5 hours (Schrenk et al. 1933). Animals exposed to BCEE vapors displayed marked signs of respiratory distress, and acute lung injury appeared to be the principal cause of death (Carpenter et al. 1949).

The acute oral LD_{50} for BCEE in rats is 75 mg/kg (Smyth and Carpenter 1948). Similar acute oral LD_{50} values (105–136 mg/kg) were reported for mice, rabbits, and rats by Union Carbide (1948). Slightly higher LD_{50} values were reported by Drake and Myer (1992) for rats (144 mg/kg) and mice (211 mg/kg). Little information exists regarding lethality following chronic oral exposure. Decreased survival was reported in female rats dosed twice a week with 50 mg/kg for 18 months (Weisburger et al. 1981). The cause of the increased mortality was not determined.

BCEE has moderate dermal toxicity, with an estimated LD_{50} in rabbits of 870 mg/kg (Union Carbide 1948). Smyth and Carpenter (1948) and Union Carbide (1948) estimated that the amount absorbed through the skin of guinea pigs leading to death in 50% of the animals was about 370–390 mg/kg.

2.3 BODY WEIGHT

A significant decrease in body weight gain was observed in both rats and guinea pigs exposed to 69 ppm BCEE via inhalation for 130 days (Dow Chemical 1958).

Weisburger et al. (1981) reported that oral exposure to doses of 25 or 50 mg/kg (twice a week for 78 weeks) resulted in decreased body weights in rats, but the magnitude of this effect was not described.

2.4 RESPIRATORY

The principal acute effect of inhalation exposure to BCEE vapor is irritation and injury to the cells of the respiratory epithelium. In humans, brief exposure to concentrations ≥550 ppm was reported to be very irritating to the nasal passages (Schrenk et al. 1933). Exposure to 260 ppm was less irritating, and irritation was considered mild at 100 ppm and minimal at 35 ppm (Schrenk et al. 1933).

Studies in guinea pigs provide similar findings, with 35 ppm producing slight nasal irritation within 10 minutes, and higher concentrations producing proportionately greater and more rapid signs of nasal irritation (Schrenk et al. 1933). Exposure to concentrations ≥105 ppm resulted in lung congestion, edema, and hemorrhage. The severity of the pulmonary lesions increased with exposure duration and concentration. Exposure of rats or guinea pigs to 69 ppm BCEE for 130 days did not result in significant changes in lung/body weight ratios, and did not lead to histological changes in lung (Dow Chemical 1958).

2.5 CARDIOVASCULAR

No histological alterations were observed in the hearts of rats and guinea pigs exposed to 69 ppm for 130 days (Dow Chemical 1958).

2.6 GASTROINTESTINAL

No human or animal studies examining gastrointestinal effects were located.

2.7 HEMATOLOGICAL

Intermediate-duration inhalation exposure of rats and guinea pigs to 69 ppm of BCEE did not result in hematological effects or histological damage to the spleen (Dow Chemical 1958).

2.8 MUSCULOSKELETAL

No human or animal studies examining musculoskeletal effects were located.

2.9 HEPATIC

No gross or histological signs of hepatic injury were observed in rats or guinea pigs exposed to 69 ppm for 130 days (Dow Chemical 1958).

2.10 RENAL

No gross or histological alterations were observed in the kidney of rats or guinea pigs exposed to 69 ppm BCEE for 130 days (Dow Chemical 1958).

2.11 DERMAL

Smyth and Carpenter (1948) reported irritation in rabbits following application of 10 mg BCEE to skin.

2.12 OCULAR

Schrenk et al. (1933) reported that a brief exposure to 550 and 1,000 ppm BCEE resulted in profuse lacrimation and was very irritating to the eyes. The severity of the irritation decreased at lower concentrations and minimal irritation was observed at 35 ppm.

In guinea pigs, exposure to BCEE in air resulted in lacrimation within 3 minutes of exposure to ≥260 ppm, but not at 105 ppm (Schrenk et al. 1933). Squinting (which is likely suggestive of eye irritation) was observed after a 20-minute exposure to 105 ppm and 1-minute exposure to 260 ppm, but was not observed at 35 ppm. Carpenter and Smyth (1946) reported that 25 mg BCEE (0.02 mL of undiluted liquid) instilled in the eye of rabbits caused moderate irritation (a grade of 4 out of 10 was assigned).

2.13 ENDOCRINE

Intermediate-duration inhalation exposure to 69 ppm did not result in histological alterations in the adrenal or pancreas of rats and guinea pigs (Dow Chemical 1958).

2.14 IMMUNOLOGICAL

No studies were located regarding immunological effects in humans or animals following inhalation, oral, or dermal exposure to BCEE. In an *in vitro* assay, dose-dependent inhalation of BALB/c mouse splenic

T-cell lymphocyte mitogenesis in response to concanavalin A was observed (Sakazaki et al. 2001). No response to lipopolysaccharide was found in C3H/He mouse splenic B-cell lymphocytes.

2.15 NEUROLOGICAL

Data from animal studies indicate that BCEE is a central nervous system depressant following inhalation exposure. Schrenk et al. (1933) observed that guinea pigs exposed to concentrations ≥105 ppm began to become lethargic and uncoordinated within several hours, and that unconsciousness and death could follow. No neurological symptoms were observed at 35 ppm. No effects on behavior were noted in guinea pigs or rats exposed to 69 ppm for 130 days (Dow Chemical 1958), but no details were provided on how behavior was evaluated.

2.16 REPRODUCTIVE

No studies were located regarding reproductive effects in humans following inhalation exposure to BCEE. In animals, no gross or histological effects were observed in reproductive tissues of rats and guinea pigs exposed to 69 ppm of BCEE for 18 weeks (Dow Chemical 1958), but no tests of reproductive function or success were performed.

2.17 DEVELOPMENTAL

No studies were located regarding the developmental effects in humans or animals following exposure to BCEE.

2.18 OTHER NONCANCER

No studies were located regarding other noncancer effects in humans or animals following exposure to BCEE.

2.19 CANCER

Innes et al. (1969) reported an increased incidence of hepatomas in two strains of mice exposed to an average oral dose of 41 mg/kg/day for 80 weeks. The effect was most marked in the males, with liver tumors occurring in 53 and 88% of the exposed males of the two strains, compared with 10 and 6% in unexposed controls, respectively. A smaller effect (22 versus 0%) was observed in females from one strain, but no effect was seen in females of the other strain. The authors of the study emphasized that

although the tumors were described as hepatomas, the majority of tumors might have had malignant potential. No increased incidence of tumors was observed in male or female rats exposed twice a week to doses of 25 or 50 mg/kg (Weisburger et al. 1981).

Van Duuren et al. (1972) performed a two-stage initiation-promotion test for tumor production in mouse skin using a single dermal dose of BCEE (as the initiator) followed by repeated doses of phorbol myristate acetate (as promotor) for 2 years. The frequency of skin papillomas in the BCEE-treated mice (3/20) was not significantly different from the control group (2/20). Tests were not performed to investigate whether BCEE had any promotor activity, or if it was carcinogenic if applied repeatedly itself.

Based on positive carcinogenicity data in the Innes et al. (1969) study and positive genotoxicity evidence, EPA (IRIS 2002) has classified BCEE in Group B2, probable human carcinogen.

2.20 GENOTOXICITY

The *in vivo* genotoxicity of BCEE, summarized in Table 2-4, has been investigated in mice and *Drosophila*. No evidence of heritable reciprocal translocation of chromosomes was observed in mice following 8-week gavage administration of BCEE (Jorgenson et al. 1978; only available as an abstract). Similarly, no increases in reciprocal translocations were observed in *Drosophila* (Foureman et al. 1994). Positive evidence of sex-linked recessive lethality was observed in *Drosophila* when BCEE was injected but not when it was administered in feed (Foureman et al. 1994). Weak positive results were found in an assay of somatic cell recombination (Ballering et al. 1996).

Table 2-4. Genotoxicity of Bis(2-Chloroethyl)Ether *In Vivo*

Species (exposure route)	Endpoint	Results	Reference
Mice (8-week gavage)	Heritable reciprocal translocation	–	Jorgenson et al. 1978
Drosophila melanogaster (inhalation)	White/white$^+$ eye mosaic recombination	(+)	Ballering et al. 1996
D. melanogaster (feed)	Sex-linked recessive lethality	–	Foureman et al. 1994
D. melanogaster (injection)	Sex-linked recessive lethality	+	Foureman et al. 1994
D. melanogaster (injection)	Heritable reciprocal translocation	–	Foureman et al. 1994

– = negative result; + = positive result; (+) = weakly positive results

In *in vitro* genotoxicity studies (Table 2-5), a positive result for mutations in *Salmonella* was found for BCEE without metabolic activation (Simmon 1977); with activation, no alterations in mutation frequency were found (Norpoth et al. 1986). In three genotoxicity assays in *Escherichia coli*, BCEE did not induce forward mutations, recombination, or SOS induction (Quinto and Radman 1987).

Table 2-5. Genotoxicity of Bis(2-Chloroethyl)Ether *In Vitro*

		Results		
		Activation		
Species (test system)	Endpoint	With	Without	Reference
Salmonella typhimurium (TA100)	Mutation	–	ND	Norpoth et al. 1986
S. typhimurium (TA100)	Mutation	ND	+	Simmon 1977
Escherichia coli (MT103)	Forward mutation	ND	–	Quinto and Radman 1987
E. coli (MT119)	Recombination	ND	–	Quinto and Radman 1987
E. coli (MT126)	SOS induction	ND	–	Quinto and Radman 1987

– = negative results; + = positive results; ND = not determined