THIOTEPA

Thiotepa was considered by a previous IARC Working Group in 1989 (IARC, 1990). Since that time, new data have become available, these have been incorporated into the *Monograph*, and taken into consideration in the present evaluation.

1. Exposure Data

1.1 Identification of the agent

Chem. Abstr. Serv. Reg. No.: 52-24-4
Chem. Abstr. Name: Aziridine, 1,1′,1″-phosphinothioylidynetris-
IUPAC Systematic Name: *tris*(Aziridin-1-yl)-sulfanylideneλ⁵phosphane
Synonyms: Phosphorothioic acid triethylenetriamide; phosphorothioic triamide, *N,N′,N″*-tri-1,2-ethanediyl-; thiophosphamide; thiophosphoramide, *N,N′,N″*-tri-1,2-ethanediyl-; Thioplex; thiotriethylenephosphoramide; *N,N′,N″*-triethylenethiophosphoramide; tri(ethyleneimino)thiophosphoramide; tri-1-aziridinylphosphine sulfide; triaziridinylphosphine sulfide; triethylenethiophosphoramide; triethylenethiophosphorotriamide; tris(1-aziridinyl)phosphine sulfide; tris(aziridinyl)phosphine sulfide
Description: Fine, white, crystalline flakes with a faint odour (McEvoy, 2007)

1.1.1 Structural and molecular formulae, and relative molecular mass
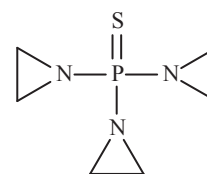
$C_6H_{12}N_3PS$
Relative molecular mass: 189.22

1.2 Use of the agent

Information for Section 1.2 is taken from McEvoy (2007), Royal Pharmaceutical Society of Great Britain (2007), and Sweetman (2008).

1.2.1 Indications

Thiotepa has been used intravesically for the treatment of residual tumours and as adjuvant therapy for prophylaxis of superficial bladder cancer. Thiotepa has also been used parenterally in the palliative treatment of adenocarcinoma of the breast and ovary. Thiotepa may be used by intracavitary injection to control pleural, pericardial, or peritoneal effusions caused by metastatic tumours.

1.2.2 Dosage

Thiotepa may be administered by intravenous, intramuscular, intrapleural, intraperitoneal, intrapericardial or intratumour injection, or by intravesical instillation.

Thiotepa may be given rapidly intravenously in doses of 0.3–0.4 mg/kg at intervals of 1–4 weeks. The drug has also been given intravenously in doses of 0.2 mg/kg or 6 mg/m^2 daily for 4 or 5 days at intervals of 2–4 weeks. Thiotepa has also been given intramuscularly in doses of 15–30 mg in various schedules.

The usual intracavitary dose of thiotepa is 0.6–0.8 mg/kg at intervals of at least 1 week, although a dose of 15–30 mg has been used intrapericardially.

For the treatment of superficial bladder tumours, the dose of thiotepa generally ranges from 30–60 mg, instilled by catheter in saline directly into the bladder. The usual course of treatment is once a week for 4 weeks. Single doses of 90 mg in 100 mL of sterile water have also been used prophylactically following local resection.

For malignant effusions, doses of up to 60 mg of thiotepa in 20–60 mL of sterile water may be instilled after aspiration; in the USA, the licensed dose is 0.6–0.8 mg/kg, a dose similar to that suggested for injection directly into tumours.

Thiotepa is available as 15 and 30 mg solutions for parenteral administration.

1.2.3 Trends in use

Although thiotepa has largely been replaced by the nitrogen mustards, it still has specific uses, particularly as a component of experimental high-dose chemotherapy regimens.

2. Cancer in Humans

Several cases of leukaemia following treatment with thiotepa alone have been reported. As was the case in the previous *IARC Monograph* (IARC, 1990), only one analytical study focused specifically on the cancer risk of thiotepa in humans (Kaldor *et al.*, 1990). This study, which used a case–control methodology within a cohort of women treated for ovarian cancer, found a strong association between the risk for leukaemia and treatment with thiotepa with a relative risk of 8.3 in the lower dose group ($n = 4$), and 9.7 in the higher dose group ($n = 5$).

3. Cancer in Experimental Animals

Thiotepa was tested for carcinogenicity by intraperitoneal administration in mice and rats, and by intravenous administration in male rats (Table 3.1).

It increased the incidence of lung tumours and malignant lymphomas in mice of each sex. In rats, intraperitoneal administration increased the incidence of lymphohaematopoietic malignancies in males and of uterine adenocarcinomas and mammary carcinomas in females. Squamous cell carcinomas of the skin or ear were also induced in both sexes. Intravenous administration to male rats induced tumours at a variety of sites (IARC, 1990).

Since the previous *IARC Monograph* (IARC, 1990), a study with CB6F1-TgH*ras*2 transgenic (*ras*H2) mice was performed during an interlaboratory validation study. Thiotepa was intraperitoneally administered to two groups of 15 male and 15 female *ras*H2 mice, 7–9 weeks of age, at doses of 1 and 2 mg/kg bw, 3 times per week for 24 weeks. Two similar groups of wild-type mice were also treated, and two groups of ten male and ten female *ras*H2 and wild-type mice served as vehicle controls. Forestomach papillomas, lung

Table 3.1 Studies of cancer in experimental animals exposed to thiotepa

Species, strain (sex) Duration Reference	Route Dosing regimen Animals/group at start	Incidence of tumours	Significance	Comments
Mouse, A/He (M, F) 24 wk Stoner et al. (1973)	i.ep. 0 (untreated), 0, 19, 47, 94 (total dose) mg/kg bw (total 12 doses) 3 ×/wk for 4 wk 100, 160, 20, 20, 20	Lung: 18/94, 48/154, 11/20, 10/19, 16/20	$P < 0.05$ (47 mg/kg bw) $P < 0.001$ (94 mg/kg bw)	95=99% pure Control groups were either untreated or treated with vehicle i.ep. 3 ×/wk for 8 wk (total 24 doses)
Mouse, B6C3F1 (M, F) 86 wk NCI (1978)	i.ep. 0, 0, 1.15, 2.3 mg/kg bw 3 ×/wk for 52 wk 15, 15, 35, 35 15, 15, 35, 35	Malignant lymphomas: M–1/18[a], 1/8, 2/24, 26/28 F–0/29[a], 0/14, 5/26, 32/32	$P < 0.001$ (2.3 mg/kg) $P < 0.001$ (2.3 mg/kg)	98 ± 1% pure
Rat, Sprague-Dawley (M, F) 86 wk NCI (1978)	i.ep. 0, 0.7, 1.4, 2.8 mg/kg bw 3 ×/wk for 52 wk 20+20, 39, 35, 35 20+20, 31, 35, 35	Myeloid leukaemia / malignant lymphomas: M–0/29[a] vs 6/34 (0.7 mg/kg) M–0/30[a] vs 6/16 (1.4 mg/kg) Skin or ear (squamous cell carcinomas): M–0/29[a] vs 7/33 (0.7 mg/kg) M–0/30[a] vs 3/13 (1.4 mg/kg) Uterine (adenocarcinomas): F–0/28[a], 7/21 (1.4 mg/kg) Mammary gland (adenocarcinomas): F–1/28[a], 8/24 (1.4 mg/kg) Skin (squamous cell carcinomas): F–0/28[a], 8/21 (1.4 mg/kg)	$P = 0.020$ $P = 0.001$ $P = 0.009$ $P = 0.023$ $P = 0.001$ $P = 0.006$ $P < 0.001$	98 ± 1% pure Analyses of the incidence in the high dose groups are not included, due to low survival for both sexes
Rat, BR 46 (M) 52 wk Schmähl & Osswald (1970), Schmähl (1975)	i.v. 0, 1 mg/kg bw, weekly for 52 wk 89, 48	Malignant tumours[b]: 4/65, 9/30 Benign tumours: 3/65, 5/30	$P < 0.01$	> 98% pure

[a] pooled control group

[b] tumours of various origin

bw, body weight; F, female; i.ep., intraepithelial; i.v., intravenous; M, male; vs, versus; wk, week or weeks

adenomas, and thymic lymphomas were induced in both treated *ras*H2 and wild-type mice. Lung adenocarcinomas were observed only in treated *ras*H2 mice. There was a higher incidence of forestomach papillomas in male *ras*H2 mice treated with 2 mg/kg thiotepa than in the corresponding wild-type mice and *ras*H2 controls. The increase in the incidence of forestomach papillomas was dose-dependent in *ras*H2 mice (Yamamoto *et al.*, 1998a, b). [The Working Group noted the limited reporting of the study, i.e., no tumour incidences were provided.]

4. Other Relevant Data

4.1 Absorption, distribution, metabolism, and excretion

In humans, intravenous injection of thiotepa results in a peak blood concentration of thiotepa within 5 minutes, and after intraperitoneal administration, the peak plasma concentration is reached within 25 minutes. Distribution of thiotepa is rapid and is followed by fast elimination from the plasma compartment, with a half-life of 1–3 hours. Triethylenephosphoramide (TEPA), a metabolite of thiotepa, is detected in plasma 5–10 minutes after intravenous injection, and persists longer in plasma with a half-life of 3–21 hours. Both thiotepa and TEPA penetrate the cerebrospinal fluid (IARC, 1990; Maanen *et al.*, 2000).

The urinary excretion of unchanged thiotepa is approximately 0.1–1.5% of the total administered thiotepa, and that of TEPA, 0.2–25%. Thiotepa can form conjugates with glutathione, and can be excreted as a thiotepa-mercapturic acid conjugate in the urine (Maanen *et al.*, 2000).

Following thiotepa administration to rodents (intraperitoneal or intravenous injection), thiotepa is distributed rapidly to different organs, with most available for metabolism in the liver

(IARC, 1990; Maanen *et al.*, 2000). Many metabolic studies of thiotepa in various species (rat, dog, rabbit, and humans) have resulted in the identification of TEPA as the major metabolite of thiotepa. The metabolism of thiotepa to TEPA is mediated by hepatic cytochrome P450 (CYP) (Teicher *et al.*, 1989; Hagen *et al.*, 1991; Chang *et al.*, 1995).

Plasma elimination of thiotepa after intravenous administration to mice follows a two-compartment model. The half-life is 0.21 minutes for the first phase, and 9.62 minutes for the second. The major urinary metabolite in rats, rabbits, and dogs following intravenous injection of ^{32}P-thiotepa is TEPA. However, most of the radioactivity in mouse urine is recovered as inorganic phosphate. TEPA is largely excreted unchanged after administration to rats, and 5–30% is converted to phosphate (IARC, 1990; Maanen *et al.*, 2000).

4.2 Genotoxic effects

4.2.1 Interaction with DNA

Both thiotepa and TEPA are alkylating agents. As alkylating agents, these compounds are potentially trifunctional. The principal site of reaction in DNA is the N^7 position of guanine. Hydrolysis of thiotepa and TEPA produces aziridine (ethyleneimine), a reactive monofunctional alkylating agent, that reacts to form 7-(2-aminoethyl)deoxyguanosine in DNA, which is an unstable adducted base that leads to depurinated sites (Musser *et al.*, 1992). An aminoethyl-N^3-adenine adduct is also formed (Andrievsky *et al.*, 1991; Musser *et al.*, 1992). Thiotepa can also act as a bifunctional alkylating agent, forming interstrand cross-links between guanine bases (at the N^7 position) of DNA (Maanen *et al.*, 2000).

In common with other alkylating agents, therapeutic cytotoxicity is accompanied by mutagenic damage (Sanderson & Shield, 1996). Thiotepa cytotoxicity is attenuated by DNA

repair, principally base-excision repair (Limp-Foster & Kelley, 2000; Kobune *et al.*, 2001; Xu *et al.*, 2001), and inhibition of DNA-repair processes enhances cytotoxicity (Frankfurt, 1991; Frankfurt *et al.*, 1993). However, lymphoblastoid cell lines derived from patients with Fanconi anaemia are hypersensitive to thiotepa (but not TEPA), implying the formation of interstrand cross-links (Cohen *et al.*, 1991). Cells that are defective in p53 are also more sensitive to thiotepa (Seo *et al.*, 2002).

4.2.2 Mutagenic effects

(a) Mutagenicity in vitro

In the previous *IARC Monograph* (IARC, 1990), it was reported that the compound induced gene mutations in *Salmonella typhimurium* and *Aspergillus nidulans*, and chromosomal aberrations and sister chromatid exchange in root meristem cells of *Vicia faba*. It also induced gene mutations, unscheduled DNA synthesis, micronuclei, sister chromatid exchange, and chromosomal aberrations in mammalian cells *in vitro*. It also induced morphological transformation of mouse cells. One study reported that thiotepa did not induce significant levels of DNA damage in rat or human testicular cells at up to 1000 μM (Bjørge *et al.*, 1996), measured as single-strand breaks and alkali-labile sites by alkaline elution.

(b) Mutagenicity in vivo

Studies of mutant frequencies in the endogenous hypoxanthine(guanine)phosphoribosyl transferase *(Hprt)* and the transgenic *LacI* gene of Big Blue rats have found that thiotepa induced more mutations in *Hprt* than in *LacI* (Chen *et al.*, 1998). The most common mutation was GC→TA transversions. *Hprt* mutations in lymphocytes were also analysed in Fischer 344 rats treated with thiotepa or TEPA, where GC→TA transversions were also the most common mutations observed (Casciano *et al.*, 1999; Chen *et al.*, 1999).

In the previous *IARC Monograph* (IARC, 1990), thiotepa induced micronuclei in the bone marrow of rats and mice, chromosomal aberrations in mouse bone-marrow and liver cells, and in peripheral lymphocytes of rhesus monkeys and rabbits. It also caused sister chromatid exchange in mouse bone marrow *in vivo*. Increased frequencies of chromosomal aberrations were observed in peripheral lymphocytes of patients receiving thiotepa therapy.

Subsequent studies have reported that thiotepa induces chromosomal aberrations in bone-marrow cells of Armenian hamsters (*Cricetulua migratorius*), although at a lower frequency than in other rodents (Nersessian, 1994).

When administered to rhesus monkeys (*Macaca mulatta*) by bolus injection, thiotepa was more cytotoxic (chromosomal aberrations in bone marrow) than when the same dose was given by continuous infusion over 96 hours (Rao *et al.*, 2005). The induction of chromosomal aberrations and sister chromatid exchange in rhesus monkeys by intravenous injection of thiotepa led to an increase of the number of both sister chromatid exchange and chromosomal aberrations 14 hours after injection after which these levels began to fall. Sister chromatid exchange frequency reached control levels after 1 month, whereas chromosomal aberration frequency remained elevated after 6 months (Kuzin *et al.*, 1989). The dietary antimutagens chlorophyllin, β-carotene and α-linolenic acid inhibited thiotepa-induced chromosomal aberrations in Chinese hamsters by up to 85% (Renner, 1990).

Thiotepa was reported previously to induce chromosomal aberrations in germ cells, sperm abnormalities, and dominant lethal mutation in mice *in vivo* (IARC, 1990). In a subsequent study, thiotepa was reported to give similar yields of dominant lethal mutations in different strains of mice (Lyon & Glenister, 1991), in contrast to earlier reports showing differences among strains (Surkova & Malashenko, 1975, 1977). Subsequent studies have also reported that thiotepa produced

very low yields of translocations in mouse stem cells (De Luca *et al.*, 1990).

Thiotepa induced chromosomal aberrations in the reproductive cells of the female yellow fever mosquito (*Aedes aegypti*) (Puttaraju, 1994).

4.3 Synthesis

Thiotepa is an alkylating agent that is carcinogenic via a genotoxic mechanism.

5. Evaluation

There is *sufficient evidence* in humans for the carcinogenicity of thiotepa. Thiotepa causes leukaemia.

There is *sufficient evidence* in experimental animals for the carcinogenicity of thiotepa.

Thiotepa is *carcinogenic to humans (Group 1)*.

References

Andrievsky GV, Sukhodub LF, Pyatigorskaya TL *et al.* (1991). Direct observation of the alkylation products of deoxyguanosine and DNA by fast atom bombardment mass spectrometry. *Biol Mass Spectrom*, 20: 665–668. doi:10.1002/bms.1200201103 PMID:1799576

Bjørge C, Brunborg G, Wiger R *et al.* (1996). A comparative study of chemically induced DNA damage in isolated human and rat testicular cells. *Reprod Toxicol*, 10: 509–519. doi:10.1016/S0890-6238(96)00138-4 PMID:8946565

Casciano DA, Aidoo A, Chen T *et al.* (1999). Hprt mutant frequency and molecular analysis of Hprt mutations in rats treated with mutagenic carcinogens. *Mutat Res*, 431: 389–395. PMID:10636003

Chang TK, Chen G, Waxman DJ (1995). Modulation of thiotepa antitumor activity in vivo by alteration of liver cytochrome P450-catalyzed drug metabolism. *J Pharmacol Exp Ther*, 274: 270–275. PMID:7616408

Chen T, Aidoo A, Manjanatha MG *et al.* (1998). Comparison of mutant frequencies and types of mutations induced by thiotepa in the endogenous Hprt gene and transgenic lacI gene of Big Blue rats. *Mutat Res*, 403: 199–214. PMID:9726020

Chen T, Aidoo A, Mittelstaedt RA *et al.* (1999). Hprt mutant frequency and molecular analysis of Hprt mutations in Fischer 344 rats treated with thiotepa. *Carcinogenesis*, 20: 269–277. doi:10.1093/carcin/20.2.269 PMID:10069464

Cohen NA, Egorin MJ, Snyder SW *et al.* (1991). Interaction of N,N',N"-triethylenethiophosphoramide and N,N',N"-triethylenephosphoramide with cellular DNA. *Cancer Res*, 51: 4360–4366. PMID:1714342

De Luca JC, Dulout FN, Ulrich MA *et al.* (1990). The induction of reciprocal translocations in mouse germ cells by chemicals and ionizing radiations. II. Combined effects of mitomycin C or thio-tepa with two doses of gamma-rays. *Mutat Res*, 232: 11–16. PMID:2117707

Frankfurt OS (1991). Inhibition of DNA repair and the enhancement of cytotoxicity of alkylating agents. *Int J Cancer*, 48: 916–923. doi:10.1002/ijc.2910480620 PMID:1907257

Frankfurt OS, Seckinger D, Sugarbaker EV (1993). Inhibition of DNA repair in cells treated with a combination of alkylating agents. *Anticancer Res*, 13: 947–952. PMID:8352564

Hagen B, Dale O, Neverdal G *et al.* (1991). Metabolism and alkylating activity of thio-TEPA in rat liver slice incubation. *Cancer Chemother Pharmacol*, 28: 441–447. doi:10.1007/BF00685820 PMID:1718615

IARC (1990). Pharmaceutical drugs. *IARC Monogr Eval Carcinog Risks Hum*, 50: 1–415. PMID:2127291

Kaldor JM, Day NE, Pettersson F *et al.* (1990). Leukemia following chemotherapy for ovarian cancer. *N Engl J Med*, 322: 1–6. doi:10.1056/NEJM199001043220101 PMID:2104664

Kobune M, Xu Y, Baum C *et al.* (2001). Retrovirus-mediated expression of the base excision repair proteins, formamidopyrimidine DNA glycosylase or human oxoguanine DNA glycosylase, protects hematopoietic cells from N,N',N"-triethylenethiophosphoramide (thioTEPA)-induced toxicity in vitro and in vivo. *Cancer Res*, 61: 5116–5125. PMID:11431349

Kuzin SM, Stukalov SV, Viktorov VV *et al.* (1989). Induction and elimination of cytogenetic disturbances in lymphocytes of monkeys exposed to thiophosphamide. *Biull Eksp Biol Med*, 107: 737–739. doi:10.1007/BF00840764 PMID:2506944

Limp-Foster M & Kelley MR (2000). DNA repair and gene therapy: implications for translational uses. *Environ Mol Mutagen*, 35: 71–81. doi:10.1002/(SICI)1098-2280(2000)35:2<71::AID-EM1>3.0.CO;2-P PMID:10712740

Lyon MF & Glenister PH (1991). A search for strain differences in response of mice to mutagenesis by thio-TEPA. *Mutat Res*, 249: 317–321. PMID:1906579

Maanen MJ, Smeets CJ, Beijnen JH (2000). Chemistry, pharmacology and pharmacokinetics of N,N',N" -triethylenethiophosphoramide (ThioTEPA). *Cancer*

Treat Rev, 26: 257–268. doi:10.1053/ctrv.2000.0170 PMID:10913381

McEvoy GK, editor (2007). *American Hospital Formulary Service Drug Information*. Bethesda, MD: American Society of Health-System Pharmacists.

Musser SM, Pan SS, Egorin MJ *et al.* (1992). Alkylation of DNA with aziridine produced during the hydrolysis of N,N',N''-triethylenethiophosphoramide. *Chem Res Toxicol*, 5: 95–99. doi:10.1021/tx00025a016 PMID:1374653

NCI (1978). *Bioassay of Thiotepa for Possible Carcinogenicity*. Technical Report Series No. 58. Washington DC: US Government Printing Office, No. DHEW Publication No. (NIH) 78–1308. Available at: http://ntp.niehs.nih.gov/ntp/htdocs/LT_rpts/tr058.pdf

Nersessian AK (1994). Clastogenic action of thiotepa on bone marrow cells of the Armenian hamster. *Mutat Res*, 322: 287–290. doi:10.1016/0165-1218(94)90104-X PMID:7523922

Puttaraju HP (1994). Meiosis and chromosomal effects of thio-TEPA in the ovarian cells of Aedes aegypti. *Cytobios*, 78: 221–226. PMID:8001399

Rao VK, Knutsen T, Ried T *et al.* (2005). The extent of chromosomal aberrations induced by chemotherapy in non-human primates depends on the schedule of administration. *Mutat Res*, 583: 105–119. PMID:15927870

Renner HW (1990). In vivo effects of single or combined dietary antimutagens on mutagen-induced chromosomal aberrations. *Mutat Res*, 244: 185–188. doi:10.1016/0165-7992(90)90070-Z PMID:2113182

Royal Pharmaceutical Society of Great Britain (2007). *British National Formulary*, No. 54. London: BMJ Publishing Group Ltd./RPS Publishing.

Sanderson BJ & Shield AJ (1996). Mutagenic damage to mammalian cells by therapeutic alkylating agents. *Mutat Res*, 355: 41–57. PMID:8781576

Schmähl D (1975). Experimental investigations with anticancer drugs for carcinogenicity with special reference to immunedepression. *Recent Results Cancer Res*, 52: 18–28. PMID:1234999

Schmähl D & Osswald H (1970). Experimental studies on the carcinogenic effects of anticancer chemotherapeutics and immunosuppressive agents. *Arzneimittelforschung*, 20: 1461–1467. PMID:5536412

Seo YR, Chen EI, Smith ML (2002). Sensitivity of p53-deficient cells to oxaliplatin and thio-TEPA (N, N', N'' triethylenethiophosphoramide). *Breast Cancer Res Treat*, 72: 255–263. doi:10.1023/A:1014913708916 PMID:12058967

Stoner GD, Shimkin MB, Kniazeff AJ *et al.* (1973). Test for carcinogenicity of food additives and chemotherapeutic agents by the pulmonary tumor response in strain A mice. *Cancer Res*, 33: 3069–3085. PMID:4202501

Surkova NI & Malashenko AM (1975). The mutagenic effect of thioTEPA in laboratory mice. IV. The influence of genotype and sex on the frequency of induced chromosome aberrations in bone marrow cells. *Genetika*, 11: 66–72. PMID:817971

Surkova NI & Malashenko AM (1977). Genetic control of mutability in laboratory mice. I. Genetic analysis of the sensitivity of mice of strains 101/H and C57BL/6 to the mutagenic effect of thio-TEPA. *Genetika*, 13: 1572–1578. PMID:413765

Sweetman SC, editor (2008). *Martindale: The Complete Drug Reference*. London: Pharmaceutical Press. Available at: http://www.medicinescomplete.com/mc/

Teicher BA, Waxman DJ, Holden SA *et al.* (1989). Evidence for enzymatic activation and oxygen involvement in cytotoxicity and antitumor activity of N,N',N''-triethylenethiophosphoramide. *Cancer Res*, 49: 4996–5001. PMID:2504483

Xu Y, Hansen WK, Rosenquist TA *et al.* (2001). Protection of mammalian cells against chemotherapeutic agents thiotepa, 1,3-N,N'-bis(2-chloroethyl)-N-nitrosourea, and mafosfamide using the DNA base excision repair genes Fpg and alpha-hOgg1: implications for protective gene therapy applications. *J Pharmacol Exp Ther*, 296: 825–831. PMID:11181913

Yamamoto S, Urano K, Koizumi H *et al.* (1998b). Validation of transgenic mice carrying the human prototype c-Ha-ras gene as a bioassay model for rapid carcinogenicity testing. *Environ Health Perspect*, 106: Suppl 157–69. doi:10.2307/3433912 PMID:9539005

Yamamoto S, Urano K, Nomura T (1998a). Validation of transgenic mice harboring the human prototype c-Ha-ras gene as a bioassay model for rapid carcinogenicity testing. *Toxicol Lett*, 102-103: 473–478. doi:10.1016/S0378-4274(98)00341-5 PMID:10022298