

**CALIFORNIA ENVIRONMENTAL PROTECTION AGENCY  
DEPARTMENT OF PESTICIDE REGULATION  
MEDICAL TOXICOLOGY BRANCH**

**SUMMARY OF TOXICOLOGY DATA  
FORMETANATE HCL**

**Chemical Code # 111 Tolerance # 276**

**SB 950 # 36**

3/14/00

Revised date 8/29/02

**I. DATA GAP STATUS**

<b>Chronic toxicity, rat:</b>	No data gap, no adverse effects
<b>Chronic toxicity, dog:</b>	No data gap, no adverse effects
<b>Oncogenicity, rat:</b>	No data gap, no adverse effects
<b>Oncogenicity, mouse:</b>	No data gap, no adverse effects
<b>Reproduction, rat:</b>	No data gap, no adverse effects
<b>Teratology, rat:</b>	No data gap, no adverse effects
<b>Teratology, rabbit:</b>	No data gap, no adverse effects
<b>Gene mutation:</b>	No data gap, possible adverse effects
<b>Chromosome effects:</b>	No data gap, possible adverse effects
<b>DNA damage:</b>	Data gap, inadequate study, no adverse effects indicated
<b>Neurotoxicity:</b>	Not required at this time

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Toxicology one-liners are attached.

All relevant record numbers through 187577 (Document No. 276-045) were examined. This includes all data on file as of 8/28/02.

In the one-liners below:

\*\* indicates an acceptable study.

**Bold face** indicates a possible adverse effect.

File name: t20020829.wpd

Original review by Aldous, 3/14/00. Revised 8/29/02 by Aldous

These pages contain summaries only. Individual worksheets may identify additional effects.

## COMBINED, RAT

\*\*276-031 069924 [Supplemental data in 276-045 187574 submitted 5/20/02] Mallyon, B. A., "T87 Technical Formetanate Hydrochloride: an evaluation of dietary oncogenic and chronic toxicity potential in the rat", Schering Agrochemicals Ltd., Chesterford Park Research Station, 5/13/88. Laboratory Project ID: TOX 84083. Fifty Crl: COBS CD (SD)BR rats/group were dosed in diet with Formetanate HCl (purity 95.1 to 96%) for 104 weeks at 0, 10, 50, or 250 ppm. An additional 20/sex/group were assigned to 12-month interim sacrifice groups. Parameters assessed included plasma and whole blood cholinesterase (ChE) inhibition at intervals, and brain ChE assays at 1-yr term for the interim sacrifice groups. Cholinesterase inhibition NOEL = 10 ppm (0.45 mg/kg/day, based on brain ChE inhibition in males). General somatic toxicity NOEL = 50 ppm (2.3 and 2.9 mg/kg/day in males and females, respectively), based on body weight decrements in both sexes. Report was classified as unacceptable, but upgradeable upon submission of dosing material analyses. The requested information was provided in Record No. 187574. Report is now acceptable, with no adverse effects. Aldous, 2/17/00 and 8/27/02.

## CHRONIC TOXICITY, RAT

(See combined, rat: above)

## CHRONIC TOXICITY, DOG

\*\* 276-028 069919 Massey, J., R. J. Harling, D. Buist, D. Crook, J. Hadley, and C. Gopinath, "T82-Formetanate Hydrochloride: dietary toxicity study in beagle dogs (final report – repeated administration for 52 weeks)", Huntingdon Research Centre, 9/19/86. Laboratory Project ID: Tox/86/197-62. [Dietary concentrations of test article are reported in 276-028 069920.] Six beagles/sex/group were dosed in diet with 0, 10, 50, or 250 ppm formetanate HCl (95.7% purity) for 52 weeks in a standard chronic study. All results were consistent with cholinesterase inhibition. An overall cholinesterase inhibition NOEL = 10 ppm (0.37 mg/kg/day), based primarily on inhibition of plasma and whole blood cholinesterases. In males, which were slightly more responsive to inhibition than females, reductions of plasma and whole blood cholinesterase activities were virtually identical for a given dose level. Inhibition typically ran about 22% and 41% at 50 ppm and 250 ppm, respectively. Secondly, clinical signs in one mid-dose dog were consistent with the pattern of cholinergic signs commonly observed at the high dose. A "chronic" NOEL of 50 ppm (1.78 mg/kg/day) reflected continuance of some clinical signs (excessive salivation, trembling, and coughing) after the initial first 3 weeks of the study. These signs were very common in high dose dogs during the first 3 weeks on study. An additional possible treatment effect was thickening of the muscular coat of jejunum (2 dogs) and pylorus of stomach (1 dog) at 250 ppm. There was no measurable change in brain cholinesterase activity. Acceptable, with no adverse effects. Aldous, 3/14/00.

## ONCOGENICITY, RAT

(See combined, rat: above)

## ONCOGENICITY, MOUSE

\*\*276-030 069922 Mallyon, B. A. "T85 Technical Formetanate Hydrochloride: an evaluation of dietary oncogenic potential in the mouse", Schering Agrochemicals Ltd., Chesterford Park Research Station, 6/24/88. Laboratory Project ID # TOX/87/197-64. [Record No. 069923 in this document contains analyses of treated diets]. Fifty CrI:CD-1 (ICR) BR mice/sex/group were dosed in diet with 0, 10, 50, or 500 ppm formetanate HCl (95.7% purity) for 95 weeks in a standard oncogenicity study. NOEL = 50 ppm (8.2 mg/kg/day), based on body weight decrements at 500 ppm, to a maximum of about 3 grams. No other treatment-related effects were evident. Acceptable, with no adverse effects. Aldous 3/14/00.

#### REPRODUCTION, RAT

\*\*276-029 069921 Tesh, J. M., "T83 Technical Formetanate Hydrochloride: The reproductive performance of rats treated continuously through two successive generations", Life Science Research Limited, 9/28/87. Laboratory Project ID # Tox 85002. Thirty CrI CD rats/sex/group were dosed with 0, 10, 50, or 250 ppm formetanate HCl in diet continuously over the course of a 2-generation study with one F0 littering period and two F1 littering periods. Apparent parental NOEL = 50 ppm (4.46 mg/kg/day), based on maternal body weight decrement during gestation of F1a litters. Developmental NOEL = 50 ppm (slight reduction in mean birth weights and in pre-weaning growth rates, and apparent reduction in pup survival). The original report was considered not acceptable, but upgradeable: DPR sought supplemental info, particularly the pilot study (Sponsor's Report No. TOX/85/197-7). This study was provided as 00276-045 187575, (see next paragraph). This pilot study justifies the dose levels used in the final study, and allows an upgrade to acceptable status. Aldous, 3/14/00 and 8/28/02.

276-045 187575 [Pilot study to 276-029 069921]. Sponsor's Report No. TOX/85/197-7 is an LSR and Schering pilot study report by Tesh, J. M. and C. R. Willoughby, dated 11/14/85, which comprises Tab 2 of this volume. CD rats (10/sex/group) were dosed with formetanate HCl in diet at 0, 50, 250, or 500 ppm for 29 days prior to pairing until about 3 weeks after delivery. Pups were killed at day 4 or day 7 post partum. Results showed dose-related decreases in plasma and whole blood cholinesterase activities in males, and in gestation body weights in females, both at 250 to 500 ppm. Highly significant findings at 500 ppm included inhibition of brain cholinesterase in both sexes, and body weight reduction in males. It is also probable that a non-significant decrease in plasma and whole blood cholinesterase was present in 500 ppm females. Aldous, 8/28/02.

#### TERATOLOGY, RAT

\*\*276-018 035821 Willoughby, C. R., E. P. Lambert, and D. J. Ford, "Technical Formetanate HCl: effects of oral administration (gavage) upon pregnancy in the rat (teratology study)", Life Science Research, 7/31/85. Sponsor Study No. TOX 84092. Twenty-two CD rats/group were dosed daily from days 6 to 15 p.c. with 0, 1, 3, or 5 mg/kg/day formetanate HCl (95.7%) in distilled water (5 ml/kg b.w.). Body weight gain was reduced in higher dose groups (gain during days 6-16 was 59 g in controls and 1 mg/kg/day groups, compared to 49 g in the two higher dose groups). Slight tremors and salivation were seen in two 3 mg/kg/day dams, just after dosing. Such signs were not noted at 5 mg/kg/day. Food consumption tended to be about 2 g/rat/day less

in the latter groups than in controls during treatment (apparent maternal NOEL = 1 mg/kg/day). There was no developmental toxicity evident (developmental NOEL \$ 5 mg/kg/day). Original DPR review requested submission of studies which justify the selected dose levels. The pilot study was submitted for this purpose (Study No. 84/SCE03/281, DPR Record No. 187576). Based on clear evidence of maternal toxicity at higher dose levels (10 and 15 mg/kg/day), the primary study is now **acceptable**. The clinical signs, body weight, and food consumption findings observed in the primary study are plausibly treatment effects, based on the pilot study. Original review by D. Shimer and C. Aldous, 3/14/00. Revised by Aldous, 8/29/02.

276-045 187576 [Pilot study, sent as supplemental data for the primary rat teratology study [Sponsor Study No. TOX 84092, DPR Document and Record Nos. 276-018 035821]. Tesh, J. M., C. R. Willoughby, and E. P. Lambert, "Technical Formetanate HCl: Effects of oral administration upon pregnancy in the rat. 1. Dose range-finding study." Study No. 84/SCE03/281, Feb. 4, 1985. Six CD (SPF) rats/group were dosed during gestation days 6-15 with Formetanate HCl at 0, 5, 10, or 15 mg/kg/day. Dams were killed at day 20 for uterine examinations. Treatment was toxic at all dose levels. Tremors, salivation, and occasional ataxia were noted at 5 mg/kg/day, and progressively more serious clinical signs were observed at 10 and 15 mg/kg/day. One 10 mg/kg/day dam and two 15 mg/kg/day dam died or were killed *in extremis* by day 10. Food consumption and particularly body weight decrements were quite remarkable at 10 to 15 mg/kg/day, and were marginally affected at 5 mg/kg/day. Distinctly low fetal weights and also very low placental weights occurred at 10 and 15 mg/kg/day. Early resorptions were increased at 15 mg/kg/day (primarily due to one litter). These findings justify the dose levels used in the primary study. Aldous, 8/29/02.

#### TERATOLOGY, RABBIT

\*\*276-018 035822 Ross, F. W., T. J. Wightman, and D. J. Ford, "Technical Formetanate HCl: effects of oral administration (gavage) upon pregnancy in the rabbit (teratology study)", Life Science Research, 7/31/85. Sponsor Study No. TOX 89094. Fourteen NZW does/group were dosed by gavage at 5 ml/kg in distilled water with 0, 5, 15, or 30 mg/kg/day formetanate HCl (96.0%) during gestation days 6-19 in a standard teratology study. High dose does displayed several cholinergic signs during the first hours after daily dosing, most commonly ataxia, increased respiratory rate, pupillary constriction, and muscular tremors. One high dose doe died shortly after treatment, presumed to be due to test article. Single incidents of ataxia in 3 mid-dose does place the maternal NOEL at 5 mg/kg/day. There was no developmental toxicity (developmental NOEL \$30 mg/kg b.wt./day). Acceptable, with no adverse effects. Aldous, 3/14/00.

#### GENE MUTATION

\*\*276-017 034268, "Technical Formetanate Hydrochloride: Mouse Lymphoma Mutation Assay", (A. G. Brown, D.B. McGregor, and C. G. Riach, Inveresk Research International, Musselburgh, Scotland, Report # 3018, 18 February 1985). L5178Y mouse lymphoma cells were exposed in triplicate for 4 hours to technical formetanate hydrochloride (96% purity) at concentrations of 0, 3, 6, 13, 20, 25, 30, 40, 50, 60, 70, or 80 : g/ml in the presence and absence of activation. Levels of 20 to 80 : g/ml without activation and levels of 40 to 80 : g/ml with activation consistently increased mutation frequencies. **Acceptable with a possible adverse**

**effect.** (Original review was by A. Apostolou and N. Hughett, 9/25/85. The present re-examination, which provides data tables but makes no changes in study status, was prepared by Green and Aldous on 2/24/00).

### CHROMOSOME EFFECTS

**\*\* 276-019 040938** Allen, J. A., P. C. Brooker, D. M. Birt, and A. Howell, "Technical Formetanate Hydrochloride: metaphase chromosome analysis of human lymphocytes cultured *in vitro*", Huntingdon Research Centre, 4/19/85. NOR-AM Study #: Tox 84071. Formetanate HCl technical, purity 95.7%, was dissolved in distilled water prior to addition to wells containing lymphocytes stimulated to divide by phytohemagglutinin in the medium for 48 hrs. Exposures of cells without S9 were 24 hr, and exposures with S9 were for 2 hr. A pre-test showed toxicity-limiting range without S9 to be between 156 and 312 : g/ml, and with S9 to be between 312 and 625 : g/ml. The primary test with S9 was negative over the appropriate range of 50 to 500 : g/ml. Primary tests without S9 were negative at 20 and 200 : g/ml, but strongly positive at 100 : g/ml. A repeat test using 60, 80, 100, 120, and 140 : g/ml without S9 gave a uniform strong positive response. Investigators appropriately concluded that formetanate HCl demonstrated clastogenic activity under these circumstances. Acceptable, with possible adverse effect. Aldous, 3/14/00.

### DNA DAMAGE

276-028 069918 "Technical Formetanate Hydrochloride: Unscheduled DNA Repair in Cultured Mammalian Cells". (J. A. Allen and R. J. Proudlock, Huntingdon Research Centre, Huntingdon, Cambridgeshire, England, Report # FSB 195/85847, 11/19/85). Technical formetanate hydrochloride (96% purity) was exposed to cultured monolayers of HeLa cells at 12 serial dilutions ranging from 30 to 61440 : g/ml, with and without metabolic activation. Concentrations were tested in duplicate with a complete repeat trial. Cells detached from coverslips at treatment levels of 3840 : g/ml and above, indicating toxicity. No increase in unscheduled DNA synthesis as measured by increases in the nuclear grain count by autoradiography was indicated. **No adverse effect indicated. Unacceptable.** Report lacked data showing cytoplasmic grain counts versus nuclear grain counts for net nuclear counts. There was no justification for using HeLa cells. (D. Shimer and C. Aldous. Worksheet finalized 3/14/00). A re-submission, effectively identical to the original record, was provided in 00276-045 187577. The associated cover letter cited the report Introduction section for justification of the use of HeLa cells. The Introduction, however, gave no meaningful justification for using HeLa cells, as opposed to diploid fibroblast cells such as WI-38. The re-submission did not provide cytoplasmic count data to provide net nuclear grain counts. Also, there was no indication of the percentages of cells in S-phase, nor how such cells were identified. It is not clear whether S-phase cells were excluded from the numbers having > 5 grains/cell. Study remains unacceptable, and does not appear to be upgradeable. Gee and Aldous, 8/29/02.

### NON-REVIEWABLE RECORDS ON SUBJECTS RELATING TO SB-950 DATA REQUIREMENTS

276-014 This volume, logged into the California Department of Agriculture Division of Inspection Services in 1969, contains only three pages of toxicology data relating to a variety of study types. Studies mentioned are unlikely to meet modern standards, and none of the brief descriptions of studies (typically about one paragraph each) give details about the authors, laboratories, or other identifiers relating to the studies. None of the descriptions identified adverse effects. Records numbers in this document include 014828, 014829, 014830, and 014831. Aldous, 2/15/00.

276-004 This volume, logged into the California Department of Food and Agriculture in 1970, contains references to numerous studies, only a small percentage of which related to human toxicity. No reviewable studies were included. The following records are identified here, because the record numbers appear on DPR library printout. Record No. 31940 (pp. 9-10) makes very brief references to one or more chronic, teratology, reproduction, and dominant lethal studies. None of these were stated to have elicited adverse effects. Several studies are mentioned in a "Toxicology – Summary" section found just following the fourth tab in the volume. References here of study types relevant to this Summary of Toxicology Data included Record No. 031953 (neurotoxicity, hen, negative), Record No. 031943 (chronic dog, 18 months duration, negative), Record No. 031946 (teratology, rabbit, negative), and Record No. 031945 (reproduction in rats and dogs, negative). This section also contains studies not normally required under SB-950, but which were listed in the DPR printout. One is Record No. 031942, which describes brief cholinergic symptoms in 3 workers exposed to high levels of formetanate HCl dusts: symptoms lasted about 3 hours, with no after-effects. Rat metabolism was briefly described in Record No. 031941 (located just before the first Tab "C-1"). Excretion was rapid, 80% via urine, and 6% in feces within 24 hr. Metabolism begins with cleavage of the amino nitrogen to form *m*-formaminophenyl-N-methylcarbamate. The carbamate group is then removed to generate *m*-formaminophenol. This product is typically acetylated to *m*-acetamidophenol prior to conjugation. A publication is found just following the second Tab "C-1", which includes a figure showing the major steps in metabolism. This is Record No. 968810, publication by A. K. S. Gupta and C. O. Knowles, "Fate of formetanate-<sup>14</sup>C acaricide in the rat", *Journal of Economic Entomology* 63:10-14. Aldous, 2/18/00.