SUMMARY OF TOXICOLOGY DATA
Iodomethane

Chemical Code # 005783, Tolerance # 52875
SB 950 # NA

Original date: 13 May 2002
Revised: 9/20/02, 9/23/02, 1/9/03, 11/21/05, 5/10/07, and 6/16/09

I. DATA GAP STATUS

Chronic toxicity, rat: No data gap, possible adverse effect indicated
Chronic toxicity, dog: No data gap, possible adverse effect indicated
Oncogenicity, rat: No data gap, possible adverse effect indicated
Oncogenicity, mouse: No data gap, possible adverse effect indicated
Reproduction, rat: No data gap, possible adverse effect indicated
Teratology, rat: No data gap, no adverse effect
Teratology, rabbit: No data gap, possible adverse effect indicated
Gene mutation: No data gap, no adverse effect
Chromosome effects: No data gap, possible adverse effect indicated
DNA damage: No data gap, no adverse effect
Neurotoxicity: No data gap, no adverse effect

Toxicology one-liners are attached.

All record numbers through 228420 (document # 52875-0115) were examined. This includes all records indexed as of 4/18/07 relevant to DPR Medical Toxicology Branch Data Review Groups.
** indicates an acceptable study.
Bold face indicates a possible adverse effect.
## indicates a study on file but not yet reviewed.
File name: t20090505.wpd
Prepared by C. Aldous, 5/10/07; C. Aldous, 6/16/09.
II. TOXICOLOGY ONE-LINERS AND CONCLUSIONS

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

**COMBINED, RAT**

**52875-0094 217697** Kirkpatrick, D. T., “A 24-month inhalation combined chronic toxicity/carcinogenicity study of iodomethane in rats,” WIL Research Laboratories, LLC, Ashland, OH, 3/29/05, Laboratory Study # WIL-418019. Sixty Crl:CD® (SD)IGS BR rats/sex/group were dosed with iodomethane at 0, 5, or 20 ppm, and 70 rats/sex were treated at 60 ppm. Of these, 10 (for 0, 5, and 20 ppm groups) or 20 (for 60 ppm group) were sacrificed at 1 year. The remaining 50/sex/group were designated for the 2-yr oncogenicity study. Exposures by whole-body inhalation were performed 5 days/wk for 6 hr/day. Test article was 99.7% iodomethane for all but 36 exposures (i.e. about 7 weeks out of the 104-week study), during which time the iodomethane purity was 97.9%, with a contamination of 2% dichloromethane. This circumstance is unlikely to have significantly altered study outcome. A cluster of excess deaths in 60 ppm rats, especially females assigned to a certain position within the exposure chamber, occurred during months 5 and 6 of the study. As a result, high dose groups had as many as 13 excess deaths during the middle part of the study. By week 91, however, survival between controls and 60 ppm females were comparable. Engineering corrections (replacing seals, checking within-chamber air flows, and changing cage placements to avoid the region associated with excessive deaths) soon stopped the differential mortality. There were no other remarkable technical problems. NOEL is slightly below 5 ppm for both sexes. Mandibular salivary gland lesions (metaplasia and/or atrophy) were on the “tails” of the respective dose-response curves for M and F at 5 ppm (incidences for metaplasia for all rats on study being 1, 4, 25, and 63 in control through high dose males, and 0, 3, 25, and 58 for corresponding females). In addition, there is an equivocal case for nasal degeneration in the olfactory epithelium in 5 ppm females being a treatment effect (below, this ¶). A major 60 ppm effect was body weight decrement (18% and 15% body weight reductions at 51 weeks in M and F compared to controls), which suggests that the high dose may have exceeded an MTD. Food consumption was correspondingly reduced at 60 ppm in M but not in F. The majority of M and F rats at 60 ppm displayed degeneration of the nasal olfactory epithelium (overall incidences in 0 to 60 ppm males of 2/60, 3/60, 8/60, and 63/70, and 0/60, 2/59, 5/60, and 60/70 in corresponding females: with degrees of lesions progressively higher in 20 and 60 ppm groups compared to controls and 5 ppm groups). About half of 60 ppm M and F also showed olfactory epithelium cyst formation, without treatment response at lower dose levels. Thyroid glands were target organs: findings included elevated follicular cell adenomas at 60 ppm (a “possible adverse effect:” incidences in controls through increasing treatment groups in M of 2/60, 2/60, 4/60, and 13/70, and for corresponding females of 1/60, 1/59, 0/60, and 3/70). There were no significant differences in follicular carcinomas. Statistically significant non-neoplastic changes of follicular tissues were also restricted to high dose males: these were increases of hyperplasia, cyst formation, and vacuolation. Ultimobranchial cyst counts in thyroid were statistically significantly elevated in M and F at 60 ppm: this increase in a congenital lesion evidently associated with treatment. Thyroid/parathyroid organ weights were more than doubled in (and only in) high dose males at both 12-month and terminal sacrifices. Hormone levels, particularly TSH, reflected thyroid histopathology. TSH was greatly increased at 60 ppm, particularly in males (about 12-fold at week 26, and over 4-fold at weeks 52 and 104). Very small (non-significant) increases in TSH at 20 ppm, generally in males, could be treatment-related, but the lack of a definitive response at 20 ppm suggests a sharp dose-response curve for TSH stimulation, as was the case for tumor induction. T4 concentrations were erratic, T3 was unaffected or marginally reduced, and reverse T3 (r-T3) was significantly elevated at weeks 52 and 104 in 60 ppm M and F. Study is acceptable, with deficiencies as indicated. Aldous, 6/9/05.
CHRONIC TOXICITY, RAT

See Combined, Rat above.

CHRONIC TOXICITY, DOG

** 0058; 209863; “A 12-Month Oral (Capsule) Toxicity Study of Iodomethane in Dogs”; (J.F. Harriman; WIL Research Laboratories, Inc., Ashland, OH; Study NO. WIL-418018; 2/16/04);

Four beagle dogs/sex/group were dosed orally with capsules of 0, 1.5, 6.0 or 12.0 mg/kg/day of Iodomethane (TM-425) (lot no. 007403, batch no. 02, purity: 99.7%) for 12 months. One male in the 6.0 mg/kg group and one female in the 12.0 mg/kg group were euthanized in extremis on study days 297 and 290, respectively. These animals exhibited clear and/or foamy material around the mouth, decreased defecation, dermal atonia, emesis, excessive drooling and injected sclera. Clinical signs included head shaking, clear material around the mouth and excessive drooling. The head shaking and excessive drooling were limited to both sexes in the 6.0 and 12.0 mg/kg groups while animals in all of the treatment groups exhibited an increased incidence in clear material around the mouth. The incidence of marked injection of the ocular sclera was evident for all of the female treatment groups. There were no apparent treatment-related effects on mean body weight, body weight gain or food consumption. An increased mean number of platelets were noted for both the high dose males and females in the hematology evaluation at 25 and 52 weeks (p<0.05). In the serum chemistry evaluation, albumin and total protein concentrations were lower to the 12.0 mg/kg males and females and for the 6.0 mg/kg males at 25 and/or 52 weeks of the study (p<0.01 or p<0.05). Cholesterol levels for both sexes in the 6.0 mg/kg and 12.0 mg/kg groups and triglyceride levels for the 12.0 mg/kg males and females were increased over the levels in the controls at both 25 and 52 weeks (NS or p<0.05). Thyroid-stimulating hormone levels were elevated for both males and females in the 12.0 mg/kg group at both 25 and 52 weeks (NS). The increased TSH levels were attributed to one male and one female in this group which demonstrated mild to severe colloid depletion and moderate follicular cell hypertrophy (male only) of the thyroid gland and minimal to mild hyperplasia of basophilic cells in the pars distalis of the pituitary gland (data for individual animals have not been submitted in this report). The mean absolute and relative thyroid weights of the 12.0 mg/kg males and females were lower than those of the controls (NS or p<0.05). The mean absolute and relative liver weights were greater for both sexes of the 12.0 mg/kg group (NS or p<0.05). Possible adverse effect: treatment-related effects on thyroid gland. Chronic NOEL: (M/F) < 1.5 mg/kg/day (based upon the increased incidence of clinical signs in the 1.5 mg/kg group). Study acceptable. (Moore, 3/18/04)
no treatment effects according to parametric ANOVA, however data for females were not amenable to parametric comparisons, as shown by non-homogeneous variances. Neither sex gave significant values in the non-parametric Kruskal-Wallis test. Since 6 mg/kg/day and 12 mg/kg/day female groups had numerically much higher mean values than corresponding controls, these groups were individually compared to controls by the Mann-Whitney test, which also found negative results. Thus there is insufficient evidence to attribute injected sclera to treatment: intergroup differences appear to arise from incidental variable distribution.

A supplementary worksheet provides data tables for clinical signs data on “injected sclera” in eyes of beagle dogs in 2 studies. In each study, dogs were exposed daily to iodomethane (99.7%) by capsule formulated in corn oil to 0.1 mg/kg total volume. Summary data are tabulated in this worksheet for the 12-month chronic study 52998-0058 209863 [WIL Study No. 418018], and for the 90-day subchronic study 52998-0040 201696 [WIL Study No. 418017]. The subchronic study had suggested that there was an increase in “injected sclera” at 1.5 mg/kg/day and above in males, and at 6 mg/kg/day and above in females, as stated in the original DPR review. Incidences of “injected sclera” in chronic study males went slightly down with treatment. There were non-significant increases in injected sclera in treated chronic study females. Thus the apparent treatment effect suggested by subchronic study males was not observed in chronic study males, and the apparent increases in subchronic study females were not exacerbated by continuing exposure. “Injected sclera” is not a reliably evident finding of iodomethane treatment. Where treated groups showed higher incidences and/or degrees of response than controls, typically the mid-dose groups had higher incidences than high dose groups. There is no change in status of either study based on this worksheet.

**ONCOGENICITY, RAT**

See Combined, Rat above.

**ONCOGENICITY, MOUSE**

**52875-0099, -0100 218698, 218699** Harriman, J. F., “An 18 month dietary carcinogenicity study of microencapsulated iodomethane in mice,” WIL Research Laboratories, LLC, Ashland, OH, 6/24/05. Laboratory Study #: WIL-418025. An associated Pathology Working Group (PWG) report found in DPR Document No. 52875-0100, Record # 218699, is considered in this review. Fifty Crl:CD®1(ICR) mice/sex/group were dosed in diet with microencapsulated iodomethane at 0, 60, 200, or 600 ppm for 78 weeks in a standard oncogenicity study, in which also serum hormones T3, T4, and TSH were assayed in term survivors in all groups due to expected thyroid activity. Microencapsulated iodomethane was received from the sponsor at about monthly intervals. Purity of the a.i. was probably about 99.7% (purity in the recent rat combined study). Estimated achieved dosages were 8, 28, and 84 mg/kg/day (M) and 10, 35, and 100 mg/kg/day (F). NOEL < 60 ppm [markedly elevated thyroid/parathyroid weights (M & F), increased colloid and cytoplasmic vacuolation in thyroid (M & F); follicular cell hyperplasia (F); decreased body weight (M); and some evidence of upper alimentary tract local irritation manifested as hyperkeratosis (in esophagus and pharynx in F, and probably forestomach in M)]. In addition, basophilic hypertrophy of the pituitary (plausibly associated with enhanced TSH production) was statistically significantly elevated in all groups of females (without evident dose-response), which could represent a secondary treatment response or a random low control value. At 200 ppm and above, additional findings included elevated TSH (M); reduced food consumption (M); and high incidence of hyperkeratosis in the esophagus, pharynx, and forestomach (M and F). Investigators appropriately considered the non-significant increase in follicular cell tumors in high dose males (2 adenomas and 1 carcinoma) to be treatment-related. Investigators noted a positive
trend in incidence of fibromas in the cervix [incidences of 0, 1, 0, and 3 in cervix of controls through high dose (or 0, 1, 0, and 4 respectively for fibromas in cervix and/or uterus)]. There were no statistically significant pairwise comparisons. The reported historical incidences of benign fibromas in uterus or cervix are very low (Charles River Laboratories, Inc. compilation in March 2000 reported 2/2812 cases in uterus, and 0/2724 cases in cervix). This historical incidence may not be an appropriate comparison to the present study, since investigators in the present study performed multiple sectioning and a variety of staining procedures capable of identifying and characterizing many more lesions than are achievable with routine single sectioning and H&E staining alone. At present there is insufficient information to determine whether the observed incidences of fibromas, particularly in the cervix, were meaningfully elevated over expected incidences in control untreated tissues under similar examination procedures. Thus, although there was no associated histopathology nor any evident mechanism to explain the findings, the possibility that the fibromas in the cervix in high dose females was treatment-related cannot be dismissed. The fibromas were small (not grossly visible), circumscribed, and without mitotic figures; hence evidently much less important than the thyroid effects of iodomethane. The study is acceptable, with the spectrum of thyroid-associated findings over the entire dose range (including plausibly treatment-related tumors in high dose males) as the primary “possible adverse effects.” Aldous, 8/8/05.

52875-0054 209161 Interim report of Document No. 52875-0099, -0100, above.

52875-0082 216077 Another interim report of Document No. 52875-0099, -0100, above.

**REPRODUCTION, RAT**

“An Inhalation Two-Generation Reproductive Toxicity Study of Iodomethane in Rats (Comprehensive Final Report)”, (Mark D. Nemec, WIL Research Laboratories, Inc., Ashland, OH., Report # WIL-418004, 6/28/02). 30 Sprague-Dawley Crl:CD® (SD)IGS BR rats per sex per group received daily 6-hour (7 days/week) whole-body inhalation exposure to Iodomethane Technical (99.7%) to target concentrations of 0, 5, 20, and 50 ppm through 2 generations (1 litter/generation). The mean analytical concentrations were 5, 20 and 50 ppm for the F0 generation and 5, 21, and 49 ppm for the F1 generation. Mg/l equivalent exposure concentrations were 0.03, 0.11, and 0.28 mg/l at 5, 20, and 50 ppm, respectively. Parental animals were exposed for at least 10 weeks prior to mating. The animals were exposed daily during mating through gestation day 20. Exposures were not performed between gestation day 21 and lactation day 4, resuming on day 5 through to weaning. During lactation, the dams were removed from their litters for the 6 hour exposure period. The F1 parental animals were not exposed between postnatal days 22 and 28 due to excessive mortality in all study groups which resulted on day 22. Mean body weights were lower for the 50 ppm F0 females during the premating and gestation periods and for the 50 ppm F1 males during the premating and for the 50 ppm F1 females during the gestation period (p<0.01). The mean relative liver weights were increased for both sexes of the 50 ppm group in both generations (p<0.01). The mean absolute and relative adrenal gland weights were decreased for both sexes in both generations of the 50 ppm group (p<0.05 or p<0.01). The mean relative thymus weights were increased for the 50 ppm males of both generations (p<0.05 or p<0.01). The mean absolute thymus weight for the F1 males was increased as well (p<0.05). There were no correlating microscopic changes. Degeneration of the olfactory epithelium (localized rather than systemic) at nasal levels II, III, and IV was slightly increased in both sexes at 50 ppm for both generations. The mean number of implantations per dam were less for the F1 50 ppm animals than that of the control (p<0.01). The
mean litter sizes for the 50 ppm group of both generations were less than the control groups
(p<0.01 for F1 generation). The mean numbers of primordial follicles and corpora lutea in the
ovaries of the 50 ppm F1 females were increased and decreased, respectively, from those of the
controls (p<0.05). The viability index for the 50 ppm pups of both generations was lower than
that of the controls with most of the pup deaths occurring within the first 24 hours as indicated by
the 24 hour survivability index. The mean body weights of the F2 20 and 50 ppm pups were less
than those of the control on post-natal days 14 and 21 (p<0.01). The mean body weight of the 50
ppm F1 males pups when balanopreputial separation occurred was less than that of the controls
(p<0.01). The mean number of days required to achieve vaginal patency for the F1 20 and 50 ppm
female pups was increased over that of the controls (p<0.05 and p<0.01). Possible adverse effect
indicated: developmental effects upon offspring. Parental NOEL: 20 ppm (0.11 mg/l) (based
upon lower mean bodyweights and degeneration of olfactory epithelium at 50 ppm);
Reproductive NOEL: 20 ppm (0.11 mg/l) (based upon reduced live litter size for both
generations of the 50 ppm group); Developmental NOEL: 5 ppm (0.03 mg/l) (based upon lower
mean body weights for the 20 ppm pups and delayed development of the 20 ppm female pups)
Study originally supplemental when interim report was reviewed (Green and Gee, 6/11/02); Study
acceptable. (Moore, 9/19/02, revised, Moore, 3/22/04)

52875-0113  228418  Nemec, M. D. This is the gestation-lactation phase of the 3 studies
reported under this record number, comprising part of a range-finding study to set dose levels for
the primary 2-generation study, Report # WIL-418004, above. Time frame of the in-life phase of
this study was Feb. to April, 2001. This study used iodomethane dose levels of 0, 25, 75, and 100
ppm for 6 hours per day during gestation days 0-20, and on lactation days 5-20. There were 15
dams/group. At 100 ppm, 12/15 dams died or were killed moribund. One 75 ppm dam died. These
deaths were attributed to treatment. The 75 ppm dams had significant body weight
decrements during gestation. Dose levels selected for the primary reproduction study were
appropriate, based on this range-finding study. This study is unsuitable for setting NOEL’s due to
the limitations of study design. No DPR worksheet is needed. Aldous, April 9, 2007.

52875-0113  228418  Nemec, M. D. This is the pre-mating phase of the 3 studies reported under
this record number, comprising part of range-finding studies to set dose levels for the primary 2-
generation study, Report # WIL-418004, above. This study used iodomethane dose levels of 0,
25, 75, and 150 ppm (the latter dose reduced to 100 ppm at day 8) for 6 hours per day for 28 days
prior to mating, continuing to sacrifice on gestation day 11. There were 10 rats/group. At 150
ppm, six males and 5 females died or were killed moribund (often preceded by clinical signs such
as piloerection, hunched appearance, hypoactivity, clonic tremors of forelimbs, repeated head
jerks, drooping eyelids, and yellow urogenital staining) during the first week. An additional 3
males and 4 females died following reduction to 100 ppm, dying between days 20 and 46,
typically following clinical signs as above. The 75 ppm dams had modest body weight and food
consumption decrements, and an apparent reduction in implantation sites and increase in pre-
implantation losses compared to controls. Dose levels selected for the primary reproduction study
were appropriate, based on this range-finding study. This study is unsuitable for setting NOEL’s
due to the limitations of study design. No DPR worksheet is needed. Aldous, April 9, 2007.

TERATOLOGY, RAT

**52875-019  185694, “An Inhalation Prenatal Developmental Toxicity Study of Iodomethane in
Rats”, (Mark D. Nemec, WIL Research Laboratories, Inc., Ashland, OH., Report # WIL-418010,
11 January 2002). 24 mated Crl:CD® (SD)IGS BR female rats per group received whole-body
inhalation exposure to Iodomethane technical (99.7%) at analyzed mean concentrations of 0 (filtered air), 5, 20, and 60 ppm daily for 6 hours seven days per week on gestation days 6 through 19. Equivalent exposure concentrations were 28, 113, and 339 mg/m³ at 5, 20, and 60 ppm respectively. Statistically significant reductions (19% and 14.5%) in bodyweight gains for gestation days 6 through 20 and 0 through 20 respectively were recorded at 60 ppm. Maternal NOEL = 20 ppm (113 mg/m³). No adverse developmental effects. Developmental NOEL = 60 ppm (339 mg/m³). Acceptable. (Green and Gee, 6/11/02).

TERATOLOGY, RABBIT

**52875-018 185693, “An Inhalation Prenatal Developmental Toxicity Study of Iodomethane in Rabbits”, (Mark D. Nemec, WIL Research Laboratories, Inc., Ashland, OH, Report WIL-418002, 28 January 2002). 24 inseminated New Zealand white female rabbits per group were exposed to iodomethane technical (99.7%) for 6 hours per day/7 days per week at mean analyzed concentrations of 0 (filtered air), 2, 10, and 20 ppm by whole body inhalation exposure on gestation days 6 through 28. Equivalent exposure concentrations were 11, 57, and 113 mg/m³ at 2, 10, and 20 ppm respectively. Because of exposure chamber space limitations, animals of each group were divided into two equal replicates of 12. Initial exposure of animals in the second replicate occurred four weeks after initial exposure of animals in the first replicate. A statistically significant reduction (47%) in bodyweight gain was recorded for gestation days 6 through 29 at 20 ppm. Maternal NOEL = 10 ppm (57 mg/m³). Adverse developmental effects include increased late resorptions, reduced numbers of viable fetuses, and lower fetal weights at 10 and 20 ppm. Fetal weights were also lower than historical control ranges at 20 ppm. No teratogenicity. Developmental NOEL = 2 ppm (11 mg/m³). Acceptable. (Green and Gee, 6/10/02).

0045; 202641; “A Phased-Exposure Prenatal Developmental Toxicity Study of Iodomethane in Rabbits”; (M.D. Nemec; WIL Research Laboratories, Inc., Ashland, OH; Study No. WIL-418023; 2/3/03); Twenty four artificially inseminated female New Zealand White rabbits/group were exposed to 0 (group 1) or 20 ppm (0.11 mg/l) of Iodomethane (batch: 02, lot no. 007403, purity: 99.7%) from day 6 through day 28 of gestation (group 2), from day 6 through 14 (group 3), from day 15 through 22 (group 4), on days 23 and 24 (group 5), on days 25 and 26 (group 6) and on days 27 and 28 (group 7). Mean maternal body weight gains were less than that of the control during times of exposure for each respective group (groups 4, 5 and 6, p<0.01 or 0.05). Food consumption was not affected by the treatment. The mean number of late resorptions per litter was greater for groups 2, 5 and 6 than that of the controls ((0): 0.1 vs. (2): 1.2, (5): 0.6, (6): 0.7). The mean number of live fetuses per litter for group 2 was lower than that of the controls (<0.05). The critical time of exposure was apparently between days 23 and 26 of gestation. Possible adverse effect: increased incidence in late resorptions. NOEL for maternal or developmental effects can not be determined. Study supplemental (non-guideline study). (Moore, 3/17/03)

[Mode of action studies below relate to the above rabbit developmental toxicity study, Record No. 185693.]

52875-0086 216255 Sloter, E. D., “Mode of action study for iodomethane-related fetotoxicity in rabbits,” WIL Research Laboratories, LLC, Ashland, OH, 1/14/05. Laboratory Study #: WIL-418032. To evaluate mode of action relative to the primary rabbit developmental toxicity study (52875-018 185693), timed-mated NZW does were dosed with iodomethane (99.7% purity) by whole body inhalation (20 ppm), typically for 6 hr exposures, for up to 4 consecutive days, beginning on gestation day 23. As a reference material to assess probable effects of iodide as a
metabolite, aq. NaI was administered (by iv infusion, 81.2 µmol/doe/6-hr treatment period) on the same schedule as iodomethane. Negative controls received filtered air in inhalation chambers on the same schedule as the iodomethane does. For each of these 3 groups, five does were sacrificed at each of 8 intervals, seven on gestation days 23-26, and the last sacrifice on day 29. Does and fetuses were generally sampled at each interval to assess thyroid hormone levels (TSH, T4, and T3) and serum iodide levels. Methylation by iodomethane (assaying S-methylcysteine from the globin fraction from RBC’s) was assessed in does and fetuses on day 26 only. Glutathione (GSH) was assayed in control and iodomethane group does and fetuses on the first exposure day (immediately after 3 hr and 6 hr of treatment), and just before and just after the day 24 treatment period. RESULTS: There were no apparent treatment-related clinical signs nor body weight effects on the does. There was a 50% incidence of late resorptions in the iodomethane group examined at day 29, but not at earlier intervals. This is consistent with findings in the primary developmental toxicity study, and was probably treatment-related. Histopathology of thyroids (the only organ evaluated microscopically) showed hypertrophy of the follicular cells and colloid depletion to be the characteristic findings. Does, evaluated only on day 26, responded more to iodomethane (2/5 with hypertrophy, 3/5 with colloid depletion) than to NaI treatment (no hypertrophy, 1/5 with colloid depletion). Fetuses were examined at 5 intervals including day 29. Iodomethane and NaI fetuses responded to similar degrees. Responses were generally progressive over time during the treatment period, with no observed changes on day 23, the majority of fetuses having minimal hypertrophy on day 24, increased degree of hypertrophy and emergence of colloid depletion on day 25, each of these more apparent on day 26, with some recovery in both treated groups by day 29 (three days off treatment). Iodomethane increased circulating iodide to at least several hundred-fold higher than controls. Iodomethane groups had roughly twice the serum iodide concentration as the concurrent NaI groups. Fetal iodide levels at a particular sacrifice interval were commonly 2-fold to over 10-fold higher than corresponding maternal levels, whether the dosing material was NaI or iodomethane. Does appeared to clear excess iodide more rapidly following high exposure than did the fetuses. Clearance in does appeared to be biphasic, with an initial phase half-life less than 6 hr, and the second phase several times longer. Levels of serum iodide in fetuses appeared to accumulate between daily treatments to a larger extent than in the does. It is difficult to ascertain further detail about disposition of iodide in does or fetuses due to limitations associated with small sample sizes, high variability, and limited sampling intervals. The most remarkable pattern in thyroid hormone evaluation was a general increase in TSH levels in fetuses, apparent on days 25 through 29, usually statistically significant for both iodomethane and NaI fetuses. In does, the only statistically significant findings were decreases in T3 levels immediately after dosing on days 23 and 24. This may have been incidental, however, since the day 26 controls had a lower T3 level than did either of the cited significant values. Methylation as assessed by S-methylcysteine concentrations suggested modest increases in iodomethane does (70 vs. 93 nmol/g globin in controls and iodomethane, respectively) and fetuses (87 vs. 131 nmol/g globin, respectively). Modest but statistically significant decreases in fetal blood GSH concentrations on days 23 and 24 in iodomethane group fetuses assessed immediately after respective dosing periods were plausibly treatment effects. Maternal blood GSH was also significantly reduced in Day 24 does. There were no consistent GSH changes in maternal nasal respiratory epithelium nor in fetal nor maternal liver. Useful supplementary data in a mode of action study addressing known effects. Gee and Aldous, 6/13/05.
Laboratory Study #: WIL-418031. [This is a supplementary study evaluating mechanisms of toxicity associated with late fetal deaths found in the developmental toxicity study: DPR Document No. 52875-018, Record # 185693, Report # WIL-418002]. Nine groups of 10 pregnant NZW does/group under the following regimens: Groups 1-7 were untreated, and were sacrificed on sequential gestation days 21 through 27. Treated does were dosed by whole-body inhalation of iodomethane (99.7% purity) at 25 ppm for 6 hr/day for 2 days (gestation days 23-24: Group 8) or for 4 days (gestation days 23-26: Group 9). Assessments included clinical signs, fetal viability and anomalies, maternal and fetal hematology and clinical chemistry (including T3, T4, and TSH in does and fetuses and estradiol and progesterone in does), maternal and fetal gross examinations, microscopic evaluation of fetal thyroids, and blood iodide levels. Glutathione (GSH) was assayed in blood and liver of does and fetuses; also in kidneys and nasal epithelia of does. S-methylcysteine adduct formation was assessed in maternal and fetal hemoglobin. Note these limitations on study design: treated rabbits were treated and evaluated in different study weeks from non-treated rabbits, only treated rabbits were held in inhalation chambers, and apparently non-treated rabbits were not fasted for periods comparable to exposure periods of treated rabbits (during which food and water were withheld). RESULTS: There were no clinical signs, however maternal body weights and food consumption were reduced in treated groups. Necropsy findings of “lung area(s) dark red” were observed in 5 treated does, but not in any other groups, thus indicating maternal toxicity. There was a modest increase in late resorptions in the two treated groups (5/group) compared to the various controls (3 or fewer per group). Epithelial vacuolation of thyroid follicular cells was observed in male and female fetuses of both treated groups. Also, decreased colloid and follicular cell hypertrophy were observed in Group 9 male thyroids and in female fetuses of Groups 8 and 9 (response increased with exposure duration). Group 9 does had slight decreases in serum inorganic components: calcium, phosphorus, and potassium. In Group 9 fetuses, the major blood chemistry alterations were organic components: elevated albumin, globulin, creatinine, cholesterol, triglycerides, HDL cholesterol, and LDL/VLDL cholesterol. There was also a marked increase in calcium and a modest decrease in chloride. Some of these fetal clinical chemistry changes extended to Group 8. Glutathione levels were remarkably reduced in the blood of Group 9 fetuses. Serum thyroid hormones were slightly altered in does (esp. Group 9) and more markedly altered in Group 9 fetuses. In does, there was slight but significant increase in TSH, a slight but significant decrease of T3, and non-significant decreases in T4. In fetuses, TSH was unaltered in Group 8, but increased over 5-fold in Group 9 (sufficient frequency and degree of elevated values to consider a sharp response). T4 levels were slightly low in Group 8, and significantly low in Group 9. Fetal T3 was significantly low in Group 8 and normal in Group 9. The overall pattern is consistent with a disturbance in thyroxin production associated with excess iodide, despite a feedback loop capable of invoking a marked increase of TSH. Iodide was elevated in treated does and fetuses by several hundred times over levels of untreated animals. In general, serum iodide levels of untreated fetuses were several-fold higher than the does, and levels of iodide in treated fetuses were more than two-fold higher than corresponding does. Aldous, June 9, 2005.

52875-0068 215227 Unaudited draft of 52875-0085 216254, above (no DPR review).

52875-0072 215238 Incomplete draft of a biomarker study supplement, evidently associated with previously reviewed studies 52875-0085 216254 or 52875-0086 216255. No DPR review.

52875-0072 215241 Incomplete draft of a biomarker study supplement, evidently associated with previously reviewed studies 52875-0085 216254 or 52875-0086 216255. No DPR review.
GENE MUTATION

**52875-021 185696**, “Bacterial Reverse Mutation Assay (Ames) with Iodomethane”, (Valentine O. Wagner, III, and Emily W. Dakoulas, BioReliance, Rockville, MD., Report # AA38UL.504004.BTL, 14 March 2001). *Salmonella typhimurium* strains TA98, TA100, TA1535, and TA1537 and *Escherichia coli* strain WP2 uvrA were preincubated (37°C) for approximately 1 hour with Iodomethane Technical (99.7%) in the presence and absence of S9 activation at 0 (distilled water), 15, 50, 150, 500, 1500, and 5000 µg per tube then plated in triplicate and incubated 48 to 72 hours. Toxicity (reduced number of revertants) was recorded with and without S9. **No increase in the reversion frequency.** Positive controls were functional. **Acceptable.** (Green and Gee, 6/10/02).

52875-021 185698, “*In Vitro* Mammalian Cell Gene Mutation Test (CHO/HGPRT Assay) with Iodomethane”, (Richard H. C. San and Jane J. Clarke, BioReliance, Rockville, MD., Report # AA38UL.782.BTL, 8 August 2001). Duplicate 25 cm² flasks of Chinese hamster ovary cells (CHO-K₁-BH₄) were treated with Iodomethane Technical (99.7%), in the presence and absence of S9, at 0 (distilled water), 25, 50, 100, 125, 150, 175, and 200 µg/ml for 5 hours. For evaluation of cloning efficiency, cells were subcultured in triplicate, incubated 7 to 10 days, fixed and counted. Additionally, for expression of the mutant phenotype, cells from each replicate were subcultured at 2-3 day intervals during the 7-10 day incubation period. Adequate positive controls included. **No increase in mutation at the HGPRT locus. Unacceptable** (no confirmation of results). (Green and Gee, 6/10/02).

CHROMOSOME EFFECTS

**52875-021 185697**, “*In vitro* Mammalian Chromosome Aberration Test with Iodomethane”, (Ramadevi Gudi and Caren Brown, BioReliance, Rockville, MD., Report # AA38UL.331.BTL, 21 August 2001). Chinese hamster ovary (CHO-K₁) cells (approximately 5 x 10⁵ cells/25 cm² flask) were treated with Iodomethane Technical (99.7%) in the absence (4 and 20 hours) and presence (4 hours) of S9 at 0 (distilled water), 25, 50, 100, 150, 175, 200, 250, 300, or 350 µg/ml. Metaphase cells were harvested and counted 20 hours after treatment initiation. 200 cells per treatment level were evaluated. **Results were positive for induction of structural chromosomal aberrations in the absence and presence of S9 and negative for induction of numerical chromosomal aberrations.** Positive controls were functional. **Acceptable.** (Green and Gee, 6/10/02).

DNA DAMAGE

**52875-021 185699**, “Mammalian Erythrocyte Micronucleus Test with Iodomethane”, (Ramadevi Gudi and Ljubica Krsmanovic, BioReliance, Rockville, MD., Report # AA38UL.123.BTL, 2 October 2001). Five or ten ICR mice per sex per group received a single intraperitoneal injection of Iodomethane Technical (99.7%) at 0 (distilled water), 25, 50, and 100 mg/kg. Bone marrow was collected 24 hours after treatment from the low dose, mid dose, and positive control animals; and at 24 and 48 hours post-dosing from the vehicle control and high dose mice. **No increase in micronucleated polychromatic erythrocytes.** Positive controls functioned as expected. **Acceptable.** (Green and Gee, 6/10/02).
Supplemental Genotoxicity Data

MUTAGENIC EFFECTS OVERVIEW

52875-0102  219526  This record applies to the brief commentary by Milesen, B. E. and T. A. McDonald, “Review of iodomethane mutagenicity studies,” Technology Services Group (TSG), Washington, DC, and Arysta LifeScience North America Corp., San Francisco, CA, July 22, 2005. This record contains, in addition to the evaluation by the above 2 reviewers, copies of 16 mutagenicity studies which pre-dated modern guidelines, and which were collected from public literature. Copies of the studies were included in alphabetical order by the reviewers. TSG concluded that the results of the unpublished studies completed in 2001 using current methodology should be used instead of older public literature studies, which pre-date modern guidelines, and which TSG contends have serious deficiencies. A U.S. EPA memo of Oct. 11, 2005 by Nancy McCarroll addressed these same reports and provided a rebuttal to many of the TSG conclusions: “Iodomethane: Review of Iodomethane Mutagenicity Studies” (MRID 46601701, Supplement to MRID 46512402). EPA considered these data to demonstrate that iodomethane is a point mutagen and a clastogen. DPR concurs with EPA in this assessment, noting that many gene mutagen studies were positive only in the presence of substantial toxicity. Brief study descriptions follow. Aldous, Nov. 9, 2005.

This document addresses iodomethane gene mutation, chromosome effects, and DNA damage in studies previously reviewed by DPR, plus newly submitted studies in DPR Document No. 52875-0102, Record No. 219526. This record includes comments from Technology Services Group (TSG) authors, B. E. Milesen and T. A. McDonald. Subsequently, U.S. EPA produced a document authored by N. McCarroll, entitled “Iodomethane: Review of Iodomethane Mutagenicity Studies” (MRID 46601701, Supplement to MRID 46512402) DP Barcode: 320478.

In this DPR review, terms TSG and EPA represent respectively the arguments of Technology Services Group and rebuttals by EPA in the cited McCarroll document.

Prior to receipt of Document No. 52875-0102, DPR had received and evaluated four studies completed in 2001 and reviewed by DPR in 2002, with the following findings:

1. Bacterial Reverse Mutation Assay Document/Record Nos. 52875-021 185696, (Wagner and Dakoulas, Report # AA38UL.504004.BTL, 14 March 2001). A modern-design assay employing Salmonella typhimurium strains TA98, TA100, TA1535, and TA1537 and Escherichia coli strain WP2 uvrA yielded no increase in revertant frequency. Positive controls were functional. Study was classified as acceptable (Green and Gee, 6/10/02).

2. In Vitro Mammalian Cell Gene Mutation Test (CHO/HGPRT Assay), Document/Record Nos. 52875-021 185698, (San and Clarke, Report # AA38UL.782.BTL, 8 August 2001). This system found no increase in mutation frequency. Positive controls were functional. Study was classified as unacceptable (no confirmation of negative results) (Green and Gee, 6/10/02).

3. In vitro Mammalian Chromosome Aberration Test, Document/Record Nos. 52875-021 185697, (Gudi and Brown, Report # AA38UL.331.BTL, 21 August 2001). Chinese hamster ovary (CHO-K1) cells were treated with Iodomethane Technical (99.7%) in the absence and presence of S9 at 0 to 350µg/ml. Results were positive for induction of structural chromosomal aberrations in the absence and presence of S9 and negative for induction of numerical chromosomal
aberrations. Positive controls were functional. Study was classified as **acceptable.** (Green and Gee, 6/10/02).

4. DNA damage evaluation using mouse micronucleus test, Document/Record Nos. 52875-021 185699, (Gudi and Kršmanović, Report # AA38UL.123.BTL, 2 October 2001). ICR mice each received a single ip injection of Iodomethane Technical (99.7%) at 0, 25, 50, and 100 mg/kg. Bone marrow was collected 24 hours after treatment from the low dose, mid dose, and positive control animals; and at 24 and 48 hours post-dosing from the vehicle control and high dose mice. There was **no increase** in micronucleated polychromatic erythrocytes. Positive controls functioned as expected. Study was classified as **acceptable.** (Green and Gee, 6/10/02).

**SUMMARIES OF INDIVIDUAL STUDIES:**

**Bacterial Mutagenicity**

Rosenkranz, H. S. and Poirier, L. A., “Evaluation of the mutagenicity and DNA-modifying activity of carcinogens and noncarcinogens in microbial systems,” *J. Natl. Cancer Inst.*, 62 (4), 873-892, 1979. Iodomethane was evaluated as one of 14 “alkylating agents” among a total of 99 total test articles. *Salmonella typhimurium* strains 1535 and 1538 were tested by colony counts, and comparative growth inhibition zone assessments were assessed in *E. coli pol A−* and *pol A+* systems. Authors used disk diffusion rather than plate incorporation exposure for both systems, in recognition of the volatility of the test article. Authors reported significant increases (about 3-fold to about 12-fold with or without S-9 over a 5-fold dose range: article p. 878) in revertants with TA 1535 (base-pair mutagen), but no response with frameshift mutant TA 1538. Mileson and McDonald considered this study to be unsuitable for mutagenicity assessment for many reasons, including scant information on methodology and criteria for designating a positive effect, uncertainties about actual exposures of test organisms (very high nominal exposure levels, coupled with uncertain and possibly high evaporation losses from disks, uncertain diffusion of remaining iodomethane from disk through agar), and uncertainties about iodomethane toxicity in the system. EPA considered this study to provide valid qualitative data indicative of mutagenic potential. DPR accepts the EPA conclusion on this study.

Simmon, V. F., K. Kauhanen, and R. G. Tardiff, “Mutagenic activity of chemicals identified in drinking water,” in *Progress in Genetic Toxicology*, Scott, Bridges, and Sobels, Eds., Elsevier/ North-Holland Biomedical Press, pp. 249-258, 1977. Authors considered iodomethane to be negative when tested in “the standard assay,” but positive when incubations were carried out in desiccators (journal p. 255 shows apparently about 3-fold increase with 50 μl/desiccator without S-9). See associated article immediately below.

Simmon, V. F., “In vitro mutagenicity assays of chemical carcinogens and related compounds with *Salmonella typhimurium ,” *J. Natl. Cancer Inst.*, 62 (4), 893-899 (1979). This screening of 101 chemicals by the Ames test found no increases of revertants in standard petri dish assays, however a footnote in the table containing iodomethane data (p. 895) noted that iodomethane was “positive when tested in a desiccator.” This was illustrated on p. 896 in a figure showing increases in revertants of about 2-fold with S-9 and about 3-fold without S-9 at about 20 μl per 9 liter
desiccator. Milesen and McDonald considered these studies to be unsuitable for mutagenicity assessment since cytotoxicity was not addressed, variabilities across reps were not presented, dose-response relationships were not well-defined, and the mutation frequencies under similar circumstances varied appreciably between the assays described in the 1977 and 1979 reports. EPA acknowledged the above concerns, however they considered the consistent positive responses with closed system tests and consistent negative results in open petri dishes as corroborating evidence that a properly designed study with a volatile agent tends to demonstrate mutagenicity. Thus these are non-guideline with meaningful information. DPR concurs with the latter observation.


Iodomethane and other test compounds were compared with epichlorohydrin as a reference compound in studies of alkylation rates with a synthetic electrophile, 4-(p-nitrobenzyl)-pyridine, and with deoxyguanosine. Iodomethane alkylation was 27% of epichlorohydrin rates with both substrates. Iodomethane was determined by investigators to be mutagenic in the *E. coli* WP2 uvrA assay (90% as active as epichlorohydrin, tested only without activation). Only these summary values were provided. Milesen and McDonald considered this study to be unsuitable for mutagenicity assessment due to very limited information in design (including the methods used to count viable cells) and scant reporting. EPA considered this study to be well-conducted although not guideline, and to be of interest because it confirmed the alkylation capability and mutagenicity of iodomethane in *vitro*, consistent with several published studies.

Takahashi, K. and Y. Kawazoe, “Potent induction of the adaptive response by a weak mutagen, methyl iodide, in *Escherichia coli,*” Mutation Research 180, 163-169, (1987). Iodomethane was found to be mutagenic at demonstrably cytotoxic levels, assayed by *E. coli* WP2 revertant cell counts. Iodomethane, considered to be a “chemoselective methylating agent,” effectively activated the *alkA* gene, but had only weak activation of the *umuC’* gene, in contrast to more reactive chemicals such as methyl methanesulfonate. Investigators proposed that iodomethane stimulated the bacterial “adaptive response” (which increases cell repair activity in the presence of methylating agents) by direct methylation of a key methyltransferase. The same authors also published a related article, “Methyl iodide, a potent inducer of the adaptive response without appreciable mutagenicity in *E. coli,***” Biochem. Biophys. Res. Comm. 144 (1) 447-453 (1987). Milesen and McDonald considered these studies to be of limited utility because they provided little information on variabilities of responses, and because mutagenicity was limited to toxic dose levels. EPA countered by noting that the present study provided a possible mechanism for iodomethane induction of the adaptive response in bacteria. EPA also noted that the these assays, performed in suspensions (so that the test article did not immediately volatilize away) showed cellular release of β-galactosidase (a marker of both adaptive and SOS responses) at much lower dose levels than the concentration determined to be cytotoxic in the unpublished Ames test submitted to fill FIFRA guidelines (Document/Record Nos. 52875-021 185696, summarized above).

**Yeast Recombinant Mutagenicity**

Simmon, V. F., “*In vitro* assays for recombinogenic activity of chemical carcinogens and related compounds with *Saccharomyces cerevisiae D3,*” J. Natl. Cancer Inst. 62 (4), 901-909 (1979). This was a screening of the 101 chemicals which were also tested in the Ames assay by this author in the immediately preceding article in this journal. The test strain is heterozygous for mutations *ade2* and *his8*. Recombinants which are homozygous for *ade2* have a red pigment, which serves
as the test endpoint. The author found iodomethane to be positive for recombinants with and without activation. Mileson and McDonald considered this study to be unsuitable for mutagenicity assessment. EPA considered this study to valid, despite use of one of the earlier-developed strains of this species, noting in particular that the treatment of suspended cultures was at temperatures which would have allowed meaningful iodomethane exposures.

A summary statement relating to genotoxicity studies in bacteria and yeast by Mileson and McDonald (p. 16 of this record) reiterated their perspective that the guideline studies [found in DPR Document No. 52875-021 and Record No. 185696], which were negative for mutagenicity, remain valid, and that the several older published studies provided in this record cannot be relied upon, due to multiple deficiencies. EPA determined from the same set of studies that there is a significant set of valid studies, all of which pre-date modern guidelines, collectively demonstrating the mutagenicity of iodomethane. DPR acknowledges that the data taken together show a consistent pattern of mutagenicity, in some but not all studies restricted to comparatively toxic exposure levels.

**Fungi Mutagenicity**

A brief reference to a negative *Aspergillus nidulans* mutagenicity test was noted in the WHO IARC Monographs on certain halogenated hydrocarbons (Vol. 41), 4-11 February, 1986. Information on iodomethane began on p. 213 of that monograph. Reference to the negative study on p. 220 of the monograph cites author as M. Duarte (1972), and notes that the study did not control for volatility of iodomethane, since survival was unaffected by treatment.

**In vitro Mammalian Mutagenicity**

(See reference to Record No. 185698, above).

Amacher, D. E. and I. Zelljadt, “Mutagenic activity of some clastogenic chemicals at the hypoxanthine guanine phosphoribosyl transferase locus of Chinese hamster ovary cells,” *Mutation Research* 136:137-145 (1984). Iodomethane appeared to increase mutation rates at moderately toxic dose levels (p. 141, at least a 5-fold increase in mutation rates associated with about a 30% decrease in survival). This particular test is considered to assess point mutations and is not considered to reflect chromosome rearrangements. Study investigators determined that iodomethane at the dose range tested was positive for point gene mutations, whereas Mileson and McDonald considered this study to be negative because the concurrent controls appeared to be relatively low, and the test response was not sufficiently higher than more typical control mutant frequencies to consider as a positive effect. EPA countered by noting that more current recommendations than the one that TSH cited recommend basically that an increase of 2- to 3-fold over the current control and out of the historical control range of the testing laboratory would meet criteria for a positive test. Thus EPA would consider this to be a positive test, as did the study authors.

**In vitro Mammalian Clastogenicity**

Research 59:61-108 (1979). MeI was mutagenic at toxic dose levels at the TK<sup>+/−</sup> locus (with or without S-9), but not with HGPRT. Greatest sensitivity was following short exposure intervals and shorter expression periods (mutagenic at 48 or 72 hr expression, but not after 144 hr expression: pp. 80-81 of article). Mileson and McDonald made the valid observation that the only positive finding at less than 90% lethality was a marginal increase with induced S-9, 4 hr exposure, and 48-hr expression (see pp. 80-81 of publication). EPA noted, however, that there were profound increases in mutant colonies as a percentage of viable colonies, which should not be overlooked. Page 102 of that report, quoted by EPA, notes that 10 randomly selected mutant colonies treated with iodomethane were tested for cytotoxicity to iodomethane. In all cases, cytotoxicity had not changed from that of parental cell populations, thus ruling out the possibility that investigator technique had selected for pre-existing sub-populations which were inherently resistant to iodomethane. DPR agrees with TSG to the extent that this study by itself is not sufficient to consider positive, but acknowledges that the proportions of mutant colonies in the presence of substantial cytotoxicity in many instances likewise does not make this study a definite negative.

Moore, M. M. and D. Clive, “The quantitation of TK<sup>+/−</sup> and HGPRT mutants of L5178Y/TK<sup>+/−</sup> mouse lymphoma cells at varying times post-treatment,” Environmental Mutagenesis, 4:499-519 (1982). This was a methods development paper which used increases in mutation frequencies of chemicals including MeI at toxic exposure levels to illustrate the utility of the “SES” [sequester, express, and select] technique. Authors accepted it as a given that iodomethane was a mutagen: their focus was on the prevalence of small (σ) colonies elicited by iodomethane (p. 510, illustration on p. 508). There was some apparent mutagenicity response at various dose levels including one which allowed 58% survival (p. 507). Only reduced data (plots) were presented. Both TSG (p. 22 of this record) and EPA considered the small colonies in this study to reflect clastogenic activity.

Moore, M. M., D. Clive, B. E. Howard, A. G. Batson, and N. T. Turner, “In situ analysis of trifluorothymidine-resistant (TFT') mutants of L5178Y/TK<sup>+/−</sup> mouse lymphoma cells,” Mutation Research 151:147-159 (1985). A plot on p. 221 indicated that MeI (without S-9) increased frequencies of colonies sharply in the dose range associated with 20% to 60% survival, with small colonies being prevalent, nevertheless large colonies appeared to have increased several-fold above controls. A figure on p. 155 of the report showed that less-toxic dose levels permitted early identification of the bimodal distribution of large and small colonies. A prevalence of small colonies with iodomethane was noted by Mileson and McDonald to be consistent with other evidences of MeI being a clastogen, to which EPA agreed.


Amacher, D. E. and E. M. Dunn, “Mutagenesis at the ouabain-resistance locus of 3.7.2C L5178Y cells by chromosomal mutagens,” Environmental Mutagenesis 7:523-533 (1985). Mutant frequency of iodomethane appeared to be elevated over controls at about 3.75 and 5 μg/ml, corresponding to 40% to 60% reductions in relative growth (p. 529). Maximum increase at about 3.75 μg/ml was about 5-fold over concurrent controls. Both large and small ouabain-resistant colonies were observed, suggesting to investigators that at least some of the mutants reflected point mutations. This publication was criticized by Mileson and McDonald on several counts,
including non-standard statistical methods, and questionable use of data for which some replicates had less than 50% survival, thus Mileson and McDonald consider this study to be negative for appropriate dose levels. EPA cited current OPPTS guidelines which stipulate that a maximum concentration in the range of 10-20% should be appropriate, in which case this should surely be considered a positive test.

**In vitro Mammalian Cell Transformation**

Oshiro, Y., P. S. Balwierz, and S. V. Molinary, “Morphological transformation of C3H/10T1/2 CL8 cells by alkylating agents,” 1981, Toxicology Letters 9:301-306 (1981). Investigators found iodomethane to be negative in this assay. Other test compounds, including MNNG and propiolactone, were responsive in this system.

Pienta, R. J., J. A. Poiley, and W. B. Lebherz III, “Morphological transformation of early passage Golden Syrian Hamster embryo cells derived from cryopreserved primary cultures as a reliable *in vitro* bioassay for identifying diverse carcinogens,” Int. J. Cancer 19, 642-655 (1977). These investigators presented data on morphological transformation in 3-methylcholanthrene (method validation) and on a large array of “known carcinogens.” Tests included several hundred control group dishes, and tens of thousands of control colonies, all of which were negative. Many treated groups of test chemicals yielded non-negative values, generally well under 10/dose. In this setting, iodomethane transformed colonies/surviving colonies were 0/400 (control), 0/624 (0.1 μg/ml), 2/609 (1 μg/ml), 1/673 (10 μg/ml), and 0/207 (100 μg/ml). This was considered by authors as a positive response. Mileson and McDonald considered this study to be deficient in several respects, and noted further that this assay is sensitive to GSH depletion. Although not stated directly, it appears that TSG considers this study to be positive, and that thiol depletion is the most likely cause of transformed colonies. This DPR reviewer considers the study to be positive for iodomethane considering the extreme rarity of control transformed colonies evident.

**In vivo DNA Adducts**

Gansewendt, B., D. Xu, U. Foest, E. Hallier, H. M. Bolt, and H. Peter, “DNA binding of methyl iodide in male and female F344 rats,” Carcinogenesis 12:463-467 (1991). Following oral exposure to [14C] iodomethane, the highest tissue uptake (dpm/mg DNA) was in stomach, followed by forestomach, with less in liver and lung. Label uptake as 7-methylguanine was 2 to 10 times higher than of O6-methylguanine. Relative tissue distributions were comparable following inhalation exposure to [14C] iodomethane, but in this case, ratios of 7-methylguanine to O6-methylguanine ranged from 1:1 to 2:1. Authors indicate that most or all of the methylation was due to *de novo* synthesis, since there was similarity of elution peaks for radiolabel in samples taken after treatment with labeled iodomethane compared with spectrophotometric peaks in the elution profile of native untreated DNA hydrolysis products (p. 466). Mileson and McDonald assert that the present study provides no useful quantitative evidence for iodomethane as a direct methylating agent, which appears to be consistent with the findings of the study authors. EPA notes the presence reported by the study authors of 7-methylguanine, O6-methylguanine, and 3-methyladenine as evidence that direct methylation of DNA may have occurred, however DPR does not see this study as providing definitive evidence of direct methylation.

Cloutier, J-F, A. Castonguay, T. R. O’Connor, and R. Drouin, “Alkylating agent and chromatin structure determine sequence context-dependent formation of alkylpurines,” J. Mol. Biol. 306:169-188 (2001). This article describes human lymphoblast adduct formation studies in which DNA alkylation is caused by a variety of agents, including iodomethane, a representative SN2 alkyling
agent. The information provided does not appear to predict the extent of alkylation which might occur in vivo, however investigators do demonstrate selective alkylation by these SN2 agents on guanine bases at the 5' ends of guanine runs.

OVERALL SUMMARIES BY TECHNOLOGY SERVICES GROUP (TSG) AND EPA:

TSG concluded that the 4 tests cited at the beginning of this review, completed in 2001 to complete FIFRA requirements, adequately characterized the mutagenic potential of iodomethane. These tests were considered to demonstrate a capability to increase structural chromosome aberrations in vitro, but iodomethane was considered by TSG to be non-genotoxic in guideline studies, hence “not likely to be genotoxic in whole animals.” Thus genotoxicity would not likely account for increased thyroid tumors which were observed in lifetime rodent studies. TSG considered the several positive point mutagen studies submitted in Document No. 52875-0102 not to be relevant in assessment of iodomethane, since these positive studies each were considered to have technical deficiencies which made them unsuitable for consideration.

The EPA assessment of the collective studies was quite different. They considered the negative Bacterial Reverse Mutation Assay to be a “No Test” because most of the test article would have volatilized prior to incubation with the bacteria (boiling point of iodomethane is 42 °C, compared with holding temperature of the top agar of 45 °C). This contention has merit, considering that studies in which iodomethane vapors had been contained by enclosure in desiccators or where test article was applied in saturated disks commonly were positive in gene mutation tests. EPA considered several of the following tests (primarily gene mutation studies) as valid, even though the studies were not conducted according to current guidelines. EPA considered iodomethane to be a point mutagen and a clastogen.

End of summaries from volume entitled “Review of iodomethane mutagenicity studies” under DPR Document No. 52875-0102, Record No. 219526.

NEUROTOXICITY

52875-022, 0039; 185700, 201574; “An Acute Neurotoxicity Study of Iodomethane in Rats” (Schaefer, G.J., WIL Research Laboratories, Inc., Ashland, OH, Laboratory Study Number WIL-418008, 1/7/02, amended, 9/30/03). 870.62. Iodomethane (Lot No. 007403 Drum 2, purity = 99.7%) was administered as a vapor in a whole-body manner to 12 Crl:CD®(SD)IGSBR rats per sex per group at exposure levels of 0 (filtered air), 0.15, 0.53, and 2.3 mg/l (analytical) (0, 27, 93, and 401 ppm, respectively) for 6 hours. One female at 2.3 mg/l died on study day 6; no other mortalities occurred during the study interval. Treatment-related decreased defecation and dried red material around the nose and mouth of both sexes at 2.3 mg/l were observed. During the FOB conducted after dosing (day 0, within 3 hours of treatment), treatment-related effects observed in both sexes at 2.3 mg/l included repetitive movement of mouth and jaws (home cage and open field observations), salivation (handling observations), hunched body (open field observations), slight gait impairment (open field observations, females only), decreased rotarod performance, and decreased body temperature (at 0.53 and 2.3 mg/l). No treatment-related effects were observed during FOB assessments conducted on days 7 and 14. Motor activity assessments on day 0 revealed a treatment-related decrease in mean total motor activity counts and in mean ambulatory motor activity counts in both sexes at 0.53 and 2.3 mg/l but no treatment-related effects on days 7 and 14. Microscopic examinations revealed no treatment-related abnormalities. No adverse effects. NOEL (M/F) = 0.15 mg/l (27 ppm) based on decreased body temperature and decreased
motor activity. Study previously unacceptable but possibly upgradeable with the submission of
data and calculations (including the standard curves) used to determine the actual exposure
concentrations of the test article. (Corlett and Leung, 5/30/02); submitted information in vol.
52875-0039, rec. no. 201574 was sufficient to document these exposure concentrations. Study
acceptable. (upgraded, Moore, 12/2/02)

**METABOLISM AND PHYSIOLOGICAL DISPOSITION STUDIES**

**52875-033 186475, “A Comparative Oral (Gavage) and Inhalation Metabolism and
Toxicokinetic Study with Iodomethane in Male Rats”, (Daniel W. Sved, WIL Research
Laboratories, Inc., Ashland, OH., Report # WIL-418007, 27 March 2002). 12 male Sprague-
Dawley Crl:CD® (SD)IGS BR rats were used per group in the main test. For the supplemental test,
3 per group were used for oral dosing and 6 per group were used for inhalation exposure. The
supplemental test was performed to address the inefficient trapping of expired carbon dioxide,
which resulted in low recovery of the oral doses in the main study. The original trapping material,
Carbo-Sorb E, was replaced with sodium hydroxide. Iodomethane Technical (99.7% purity)
labeled with radiolabeled iodomethane (14C-CH3I) with deionized water (oral) or air (inhalation)
was used as test substance. The oral dosing animals received a single gavage dose at 1.5 or 24
mg/kg in the main test and 1 or 35 mg/kg in the supplemental. Inhalation groups received single 5
½ hour whole-body exposures at 25 (141 mg/m³) or 233 ppm (1317 mg/m³) main test and 21 (119
mg/m³) or 209 ppm (1181 mg/m³) supplemental. Main test treatment groups were sub-divided into
3 groups of 4 animals for scheduled necropsy. The first group were necropsied 0 hr (inhalation) or
1 hr post-dosing; the second at 6 hours; and sub-group three at 168 hours. In the supplemental
test, inhalation exposure groups were further divided into sub-groups of 3 animals. Half the
inhalation sub-groups were necropsied immediately after exposure. The oral groups and the
remaining inhalation sub-groups were necropsied 48 hours post-exposure. Expired air and urine
were collected 0-6, 6-12, and 12-24 hrs post-dosing/exposure, then daily through 168 hrs. Group
mean recoveries (% of dose) following oral dosing in the main test were 82.6% and 65.4% at 1.5
and 24 mg/kg respectively. Values for the supplemental test were 104.9% and 123.5% at 1 and 35
mg/kg respectively. Inhalation exposure recoveries were 56.3% and 54.4%, main test, and
104.8% and 91.4%, supplemental, at the low and high dose levels respectively. Carbon dioxide
was the major route of elimination. Approximately 50-60% of the oral dose and 40-47% of the
inhaled dose was eliminated as CO2 in 48 hours post-treatment. Urinary elimination accounted for
30-35% of administered dose through 168 hours post-treatment. Fecal elimination accounted for
2%. After oral dosing, concentrations of iodomethane equivalents in blood peaked at 4 hours and
then began to decrease. Blood levels remained relatively constant through 2 hours post inhalation
exposure and then began to decrease. Blood concentrations were greater following inhalation
exposure versus oral dosing with liver metabolism the likely mediating factor. Tissue
concentrations of iodomethane equivalents were similar to or lower than the concentration in blood
following oral dosing (except liver and GI tract) and higher than blood levels after inhalation
exposure. Major urinary metabolites (via methylation) include S-methyl glutathione and N-
(methylthioacetyl) glycine. Minor urinary metabolites were identified as methylthioacetic acid; S-
methyl cysteine; and methyl mercapturic acid. 6 - 12 hours post-treatment was the peak time of
elimination. Acceptable. (Green and Gee, 6/11/02)

52875-0112 228417 Sved, D. W., “A comparative oral (gavage) and inhalation metabolism and
toxicokinetic study with iodomethane in female rats,” WIL Research Laboratories, LLC, Ashland,
OH, 2/21/03. Laboratory Study #: WIL-476001. Twelve Crl:CD® (SD)IGS BR female
rats/route/dose were treated once with iodomethane (purity of unlabeled a.i. 99.7%; purity of
labeled a.i. not stated, but apparently similarly pure as indicated by a single sharp peak by HPLC with radio-detection, and an MS profile analogous to unlabeled a.i.). Treatment was by gavage with 1.7 mg/kg or 21 mg/kg $^{14}$C-CH$_3$I in water, or by whole-body inhalation for 6 hr at 24 ppm or 250 ppm. Of each set of 12 rats, subgroups of 4 were killed at 0 hr (inhalation) or 1 hr (oral) after treatment; or 6 hr or 168 hr after treatment (both routes). Blood was collected at intervals from the various subgroups to provide samples at 0 or 1 hr, and 2, 4, 6, 12, 24, 48, and 168 hr after treatment for plasma and RBC radiolabel analyses. Protocol tissues were analyzed at termination for radiolabel. The 168-hr subgroups were housed in metabolism cages for collection of urine, feces, and of CO$_2$ or organic labeled carbon. [The latter was presumed to be $^{14}$CH$_3$I because it was volatile and could be captured tripropylamine/DMSO traps. These samples were subjected to scintillation counting without further processing]. The largest elimination component was recovered as exhaled $^{14}$C-CO$_2$, for an estimated 53% and 73% of administered dose after low and high dose oral administration, and 40% and 47% of administered dose after inhalation exposure (note that total recovery was much larger than theoretical for the high dose oral group). Urinary label was nearly as large, accounting for 38% and 43% of label after oral dosing, and 34% and 36% of dose after inhalation treatment. Small contributions to recovered label were organic vapor (1-3%) and feces (1-4%). Most of the urinary excretion and most $^{14}$C-CO$_2$ recovery, regardless of dose and route, occurred within 12 hr of dosing. Fecal elimination, noted above to be much smaller in amount, was diminishing by 24 or 48 hr. Plasma $^{14}$C residues cleared much more quickly than RBC $^{14}$C label. Following oral administration at 1.7 mg/kg, $T_{\text{max}}$ was 4 hr, and the initial and terminal plasma elimination phase $T_{1/2}$ estimates were 5.7 hr and 54 hr, respectively. Corresponding $T_{\text{max}}$ and respective phase $T_{1/2}$ estimates for the 21 mg/kg oral group were 6 hr, 16.2 hr, and 43 hr. These values for inhalation exposures were: (24 ppm) 0 hr, 4.3 hr, and 56 hr, and (250 ppm) 2 hr, 9.3 hr, and 51 hr. For RBC kinetics, the $T_{\text{max}}$ and initial and terminal elimination phase $T_{1/2}$ estimates were: (1.7 mg/kg, oral) 4 hr, 3.6 hr, and 261 hr, (21 mg/kg, oral) 4 hr, 3.3 hr, and 223 hr, (24 ppm, inhalation) 0 hr, 2.3 hr, and 250 hr, and (250 ppm, inhalation) 2 hr, 5.7 hr, and 199 hr. No single organ strongly concentrated label compared to others at the same sacrifice interval. The very low concentration in abdominal fat compared to other tissues suggests that there is very little inert lipophilic residue of iodomethane. Peaks of major metabolites were characterized by MS, but not quantified. Compounds identified by MS were methylthioacetic acid, methylthiopyruvic acid, S-methylcysteine, S-methylcysteine-S-oxide, N-(methylthioacetyl)glycine, methylmercapturic acid, methylmercapturic acid sulfoxide, and methylglutathione. This is a useful complementary study to the earlier companion study in males, found in Record No. 186475 (Document No. 52875-0033), which was determined by DPR to be acceptable for metabolic characterization. Aldous, 3/21/07.

52875-023 Interim report for 186475; Not reviewed (Gee, 6/11/02).

52875–0070 215230 Thrall, K. D., A. D. Woodstock, J. J. Soelberg, and R. A. Corley, “Studies supporting the development of a PBPK model for methyl iodide: uptake of MeI by the rabbit nasal cavity,” Battelle, Pacific Northwest Division, Richland, WA, Nov. 10, 2004. Battelle Project No. 47542. Nine anesthetized female NZW rabbits were maintained in sealed glass chambers. Each rabbit had a tube (about 1 mm outer diameter) placed into the nose for sampling gases. The tube extended 6.5 cm from the tip of the nose, the opening presumed to be in the nasopharnx. A plethysmograph assessed breathing frequency, tidal volume, and allowed calculation of minute volume. The differences between mean iodomethane concentration in the chamber (assessed by GLC with electron capture detector) compared to concentration from the sampling tube in the nasal cavity (assessed by mass spectrometry) were used to compute the amount of iodomethane scrubbed in the nose upstream from the inlet to the sampling tube. Investigators estimated that 72% of iodomethane was scrubbed by that point, irrespective of initial chamber iodomethane
concentration (which ranged from 1.6 to 65 ppm). It did not appear that iodomethane concentration affected tidal volume, breathing frequency, or minute volume. Useful supplementary data. Green and Aldous, June 9, 2005.

52875–0070 215231 Thrall, K. D., A. D. Woodstock, J. J. Soelberg, and R. A. Corley, “Studies supporting the development of a PBPK model for methyl iodide: uptake of MeI by the rat nasal cavity,” Battelle, Pacific Northwest Division, Richland, WA, Nov. 10, 2004. Battelle Project No. 47542. Six anesthetized male SD rats were maintained in sealed glass chambers. Each rat had a tube (about 1 mm outer diameter) placed into the nose for sampling gases. The tube extended 2 cm from the tip of the nose, reaching to the nasopharynx. A plethysmograph assessed breathing frequency, tidal volume, and allowed calculation of minute volume. The differences between mean iodomethane concentration in the chamber (assessed by GLC with electron capture detector) compared to concentration from the sampling tube in the nasal cavity (assessed by mass spectrometry) were used to compute the amount of iodomethane scrubbed in the nose upstream from the inlet to the sampling tube. Investigators estimated that about 63% of iodomethane was scrubbed by that point, using an initial chamber iodomethane concentration of about 1.1 ppm. Useful supplementary data. Green and Aldous, June 9, 2005.

52875–0070 215232 Thrall, K. D., A. D. Woodstock, J. J. Soelberg, and R. A. Corley, “Studies supporting the development of a PBPK model for methyl iodide: in vivo gas uptake in rabbits,” Battelle, Pacific Northwest Division, Richland, WA, Nov. 10, 2004. Battelle Project No. 47542. Non-anesthetized female NZW rabbits were exposed to iodomethane in chambers as described in record 52875–0070 215230. The present study did not employ plethysmography. Investigators did not record clinical signs data on the rabbits, however test animals were considered to have stayed calm during the 4-hr exposure periods. Only chamber concentrations were recorded in this study. Non-specific loss of iodomethane in the chamber was estimated to be less than 5%/hr. Additional non-specific loss to the body of a single deceased rabbit was estimated to be 9% over 4 hr. Chamber concentrations over approximately 4-hr periods were reported for seven rabbits, with initial concentrations of 1.2 to 55.9 ppm. Remaining concentrations after 4 hr averaged less than 10% of initial concentrations, regardless of exposure level. An effort to use some rabbits pre-treated with diethyl maleate, apparently to retard metabolism of iodomethane, was unsuccessful due to death or distress of rabbits, therefore such pre-treatment was not utilized together with iodomethane. Useful supplementary data. Green and Aldous, June 9, 2005.

52875–0070 215233 Corley, R. A., K. R. Minard, L. L. Trease, and H. E. Trease, “Studies supporting the development of a PBPK model for methyl iodide: magnetic resonance imaging and computational fluid dynamics simulations of rabbit nasal airflows,” Battelle, Pacific Northwest Division, Richland, WA, Nov. 10, 2004. Battelle Project No. 47542. This study was designed to characterize the 3-dimensional structure of the rabbit airways, and then to use computational estimates of flow patterns to predict the percentages of inhaled air expected to pass through dorsal vs. ventral regions of the nose, and to characterize inter-individual differences in flow patterns. Three untreated female NZW anesthetized rabbits were treated with Magnevist® (a contrast medium for MRI) about 10 min prior to sacrifice, removal of the head, and imaging of the head by MRI to reveal the three-dimensional structures of the nasal passages. Fluid dynamics models were used to estimate flow patterns at a resting ventilation rate. A consistent estimate of about 20% of flow was determined to pass through the dorsal olfactory region, with the balance of flow in the rearward part of the nose moving through the ventral respiratory region. This consistency was despite appreciable inter-animal differences in flow patterns in the rostral parts of the nose, which patterns were influenced in part by local blockages or asymmetry of the ethmoid turbinates. These flow and exposure patterns were evaluated in an effort to associate nasal regional toxicity with regional exposure. Useful supplementary data. Green and Aldous, June 9, 2005.
Corley, R. A., K. R. Minard, S. Kabilan, D. R. Einstein, A. P. Kuprat, J. R. Harkema, J. S. Kimbell, M. L. Gargas, and J. H. Kinzell, “Magnetic resonance imaging and computational fluid dynamics (CFD) simulations of rabbit nasal airflows for the development of hybrid CFD/PBPK models,” Inhalation Toxicology 21(6):512-518 (2009). This article was published 5 years after a related unpublished report was submitted in support of methyl iodide (DPR Document No. 52875-0070, Record No. 215233). Both reports provided estimated nasal air flow estimates on the same three female rabbits, however only two authors (Corley and Minard) were credited on both reports. Basically, investigators recreated the 3-dimensional geometry of key slices of nasal passages using iv-injected gadopentetate as a contrasting agent and magnetic resonance imaging to visualize the boundaries of the passages. They then made calculations of air flow based on observed nasal structure. Both reports described the main airflow pattern in rabbits to enter the dorsal maxilloturbinates before eventually being in a ventral direction toward the nasopharynx. Record 215233 had estimated air flow in four compartments, roughly defined on the horizontal plane by the ventral border of the olfactory regions, and on the transverse plane by the border of the dorsal respiratory and dorsal olfactory regions. That study found the airflow-splits to be about 38% to 62% in the anterior dorsal and ventral compartments, and about 21% and 79% in the posterior dorsal and ventral compartments, respectively. The 2009 published article estimated fluxes of inhaled air reaching dorsal or ventral portions of specified planes defined by epithelial type, rather than the 4 compartments defined by parallel vertical planes and a single horizontal plane described in the 2004 unpublished report. The 2009 article also provided surface areas and air volumes in the areas of the slices. Based on the 2009 publication, air first entering from the nares passes primarily (92%) into the dorsal respiratory region: the balance enters the ventral respiratory region. At a transverse plane defined by transition of the dorsal respiratory to dorsal olfactory epithelium, about 47% of flow enters the dorsal olfactory region, vs. 53% entering the ventral respiratory (indicating ventral migration of the main air flow). Toward the posterior, at a plane dividing the dorsal olfactory regions “1” and “2,” investigators determined that nearly 99% of airflow had been channeled ventrally toward the nasopharynx. Thus only about 1% of air flow passed into posterior range of the dorsal olfactory region, despite the large surface area in this region. This information, when coupled with information about the diffusion of agents (such as MeI) across the various epithelia, and perhaps with validation of air flow predicted by this model, could yield valuable insights into exposures via the respiratory system. Useful supplementary data. Aldous, 6/16/09.

52875–0070 215234 Morris, J. E., L. B. Sasser, J. A. Creim, K. D. Thrall, and R. A. Corley, “Studies supporting the development of a PBPK model for methyl iodide: the pharmacokinetics of sodium iodide (NaI) in pregnant rabbits,” Battelle, Pacific Northwest Division, Richland, WA, Nov. 10, 2004. Battelle Project No. 47542. Two groups of 21 timed-pregnant NZW does were administered $^{131}$I-NaI at 0.75 or 10 mg/kg in a single iv injection. Three does/group were sacrificed at 0.5, 1, 2, 4, 6, 12, or 24 hr after dosing. Does and up to 3 fetuses/doe were evaluated at each interval for radioactivity in blood, plasma (does), skin (does), thyroid (does) or “thyroid plus trachea” (fetuses), trachea (posterior to the thyroid, hence free of thyroid tissue: fetuses), amniotic fluid (fetuses), and stomach contents. From at least 4 hr onward, blood concentrations in fetuses were 2 to 4-fold higher than does, regardless of dose. The relative concentration of label in maternal thyroids compared to the other tissues in 10 mg/kg does increased over time to about 20-fold over other tissues by 24 hr. In low-dose does, the relative concentration in maternal thyroids by 24 hr was over 100-fold higher than any other maternal tissues evaluated. Thyroids in fetuses did not have greater affinity for label than the associated trachea. “Stomach contents” were the predominant measured reservoir of label in fetuses. In does, skin typically had the highest label content other than thyroids, and skin label diminished over time. The percent of maternal dose found in fetuses, compared to maternal tissues other than thyroid, grew larger over the 24-hr
assessment period: this was particularly evident in the low dose group. Useful supplementary data. Green and Aldous, June 9, 2005.

52875-0096  218692 Sweeney, L. M., and M. L. Gargas, “Data and references to support the derivation of human toxicity reference values for methyl iodide using physiologically based pharmacokinetic (PBPK) modeling,” Project No. 34503, 4/29/05. Much of this record dealt with nasal MeI uptake modeling, and particularly with the relevance of active fetal concentration of inorganic iodide in rabbits and some other species compared to rats and humans. This was a rebuttal document to a variety of U.S. EPA concerns, and provided the following conclusions. Investigators considered that GSH half-lives in a given tissue should not be adjusted for interspecies differences in GSH concentrations in that tissue. For nasal variability modeling to assess the human equivalent concentration (HEC) corresponding to animal surrogates, U.S. EPA had proposed using an uncertainty factor of 2.0 for intraspecies variation, times 1.5 for sensitivity of children compared to adults. In contrast, investigators considered it sufficient to assess exposure to the most vulnerable subpopulations, such as 3-month old or 12-month-old children, and apply the 2-fold intraspecies variation to them. This would make a child-to-adult factor unnecessary. Page 6 provides sensitivity coefficients for various parameters which would affect human plasma iodide AUC model estimates. Most of the rest of the investigators’ report addresses the weight of evidence that human fetuses do not concentrate iodide, consistent with rat but in contrast to the rabbit. Little or no information exists on human fetal blood iodide levels, however there is some basis for bridging from what is known about rabbit and human tissue concentrations of iodide. Rabbit fetal serum and the fetal portion of the rabbit placenta have similar iodide concentrations, both being several times higher than the maternal portion of the placenta. Fetal rats have lower serum iodide levels than the maternal serum. Several cited investigators indicated that the human placenta is “freely permeable” to iodide. An article by C. A. Gorman, included in this record, cites other work indicating that in humans, “Iodine readily crosses the placenta, and the concentration of iodide in the fetal blood increases throughout gestation until it is approximately 75% of that in the maternal blood.” Thus developmental toxicity demonstrated in rabbit is likely to exaggerate human developmental risks by several-fold. No DPR worksheet. Aldous, Aug. 2, 2005.

52875-0096  218693 Sweeney, L. M., and M. L. Gargas, “Age-specific HECs for potential nasal effects of MeI in children: Supplement to (PBPK) modeling (MRID 46446901),” Project No. 34503 (continued), 3/29/05. Authors use previously obtained information on glutathione (GSH) depletion in the nasal areas of rats, plus comparisons of rat and human airway structural features and comparative physiological data to determine HEC’s of 4.2 ppm (for children of 3 months or 1 year) to 6.3 ppm (for adults). Previous studies had indicated that GSH depletion is a necessary condition for toxicity in the upper airway. This report contains a spreadsheet on p. 5 showing various input data and derived numbers, but does not provide the formula to derive the HEC’s. Report includes a replication from recent poster, plus two journal articles. No DPR worksheet. Aldous, Aug. 3, 2005.

52875-0096  218694 Sweeney, L. M., “Revision of HEC for nasal effects of methyl iodide (MeI): Supplement to (PBPK) modeling (MRID 46408801),” Project No. 34503 (continued), Dec. 10, 2004. An estimate of human blood flow to the maxillary sinus of 0.26 μl/cm²/sec had been obtained by Drettner and Aust (1974: one of several articles reproduced in this record). Iodomethane investigators used this value as representative of nasal epithelial surface area, and scaled it on a per-surface-area basis for all nasal passages. These estimates led to an adult HEC for nasal effects from a 24-hr period of 6.3 ppm (see Record No. 218693, which uses this derived value to estimate HEC’s for various ages of humans). No DPR worksheet. Aldous, Aug. 3, 2005.
52875-0096  218695  Sweeney, L. M., and M. L. Gargas, “Supplemental information regarding human fetal and maternal iodide AUC sensitivity and a rabbit model sensitivity analysis: Supplement to (PBPK) modeling (MRID 46446901),” Project No. 34503 (continued), 5/23/05. This record identifies the various sensitivity coefficients utilized to determine an uncertainty factor for variability in sensitivity between humans. The proposed uncertainty factor, based on the ratio of the 95th percentile AUC to the median AUC was 1.7. A table of uncertainty factors was also included relating to fetal and maternal plasma iodide AUC determinations. No DPR worksheet. Aldous, Aug. 3, 2005.

52875-0118  230153  Rayburn, W. F., A. Robinson, L. E. Braverman, X. He, S. Pino, M. L. Gargas, L. M. Sweeney, and B. E. Mileson, “Iodide concentrations in matched maternal plasma, cord plasma, and amniotic fluid from term and pre-term human pregnancies (Supplemental to MRID No. 46446901),” Conducting Laboratories: Department of Obstetrics and Gynecology, Albuquerque, NM; Iodine Research Laboratory, Boston, MA; The Sapphire Group, Dayton, OH; and Technology Sciences Group Inc., Washington, DC, Jan. 11, 2007. Laboratory Study #: 06-240. The main part of this study was evaluation of a set of matched plasma samples from 103 mothers and cord plasma samples of their live-born infants. Samples were analyzed for iodine (total iodine, with differentiation of protein-bound iodine, and inorganic iodine). The key emphasis was inorganic iodine in cord plasma vs. maternal plasma. Maternal plasma inorganic iodine ranged from 0.3 to 5.6 μg/dL, with a mean of 1.51 (SD = 0.669). Cord plasma inorganic iodine ranged from 0.3 to 4.5 μg/dL, with mean of 1.59 (SD = 0.672). The cord/maternal inorganic iodine ratio had a range of 0.35 to 4.5 μg/dL, with a mean of 1.19 (SD = 0.640). There was a general increase in the maternal/cord plasma inorganic iodide ratio with gestational age at delivery. For deliveries considered “premature” (36 weeks or earlier, N = 26) the mean ratio was 0.91; for deliveries during gestational weeks 37-41 (all ages above “premature,” N = 77), the mean ratio was 1.28. This study confirms that human infants sequester inorganic iodine only marginally above their mothers (by about 20%). By contrast, untreated rabbit fetuses have been shown to concentrate inorganic iodide markedly compared to the maternal blood. [See study: (DPR Document No. and Record No.) 52875-0085  216254, Sloter, E. D., “A combined baseline/inhalation exposure study of iodomethane-related fetotoxicity in rabbits,” WIL Research Laboratories, Inc., 1/14/05, Laboratory Study #: WIL-418031.] That study evaluated inorganic iodide in serum samples. In untreated litters evaluated at gestation days 24 or 26, fetal serum inorganic iodide was concentrated about 9-fold compared to the serum in the does. After administration of 25 ppm iodomethane for 2 or 4 days, high concentrations of inorganic iodide was found in does and fetuses, with concentrations in fetal serum about 2-fold higher than in the serum samples of the does. The primary rabbit developmental toxicity study found elevated resorptions at 10 to 20 ppm of iodomethane, with a NOEL of 2 ppm. Based on Record No. 216254 above, it would appear that these fetuses also were concentrating inorganic iodide at least two-fold above the mother animals. These data indicate that rabbit developmental toxicity NOEL’s probably reflect exaggerated perinatal toxicity compared to humans for effects attributable to excessive inorganic iodide in the blood by a factor of about 2 for high exposures, and by larger factors for small environmental exposures. These concentration factors appear relevant for interpretation of animal developmental toxicity studies serving as surrogates for human developmental toxicity hazard assessment. Useful supplementary data. Aldous, 2/27/07.

Mechanistic Studies
52875–0070  215235  Poet, T. S. and H. Wu, “Studies supporting the development of a PBPK model for methyl iodide: in vitro GSH conjugation study in rat, rabbit, and human blood and tissues with methyl iodide,” Battelle, Pacific Northwest Division, Richland, WA, Nov. 10, 2004. Battelle Project No. 47542. This study assessed the disappearance of iodomethane from the
headspace of sealed vials containing cytosol prepared from liver, kidneys, olfactory epithelium, and respiratory epithelium of pregnant NZW rabbits, liver and kidneys of pooled rabbit fetuses, liver and kidneys of male SD rats, and liver and kidneys of female human donors. Maternal rabbit olfactory epithelium showed exceptionally high metabolism of iodomethane (i.e., high $V_{\text{max}}$ values) under test conditions (in the presence of excess GSH). Fetal tissues, in contrast, were inefficient (liver) or apparently incapable of metabolism (kidney), as evidenced by low $V_{\text{max}}$ values. Other values were intermediate, with specific activity in liver consistently higher than for kidneys. Human liver cytosol values were highly variable, with one liver sample having an extremely low $V_{\text{max}}$ value. It is not clear whether this case represented quality control problems with the samples (which were purchased from an outside source), or whether this represented an individual non-conjugator. The present study did not assess the availability of reduced GSH in the evaluated tissues. Useful supplementary data. Green and Aldous, June 9, 2005; edited by Aldous 5/5/09.

52875–0079 216073 Gannon, S. A., “Iodomethane: in vitro partition coefficients in rat and rabbit tissues and human blood,” E. I. DuPont de Nemours and Company, Newark, DE, 12/14/04. Laboratory Study #: DuPont-15617. This study assessed the partition of iodomethane between tissue samples and headspace air in septum-sealed vials. Tissues assessed were blood (rat, maternal and fetal rabbit, male and female human); brain, fat, kidney, liver, muscle, nasal tissue, and thyroid (each of the latter series in rat and rabbit); and placenta (rabbit). Generally, tissues were minced, then portions of about 0.2 to 0.25 ml were placed in vials of 10.85 ml volume. Vials were charged with iodomethane (10,000 ppm), and held at 37°C (or 30°C for nasal tissue and saline samples) for 3 hr. Headspace samples were periodically assayed for iodomethane by GLC, and estimates of time zero tissue concentrations were made by projecting from the tissue concentration values over time. Partition coefficients for fat were quite high (89 in rat, 87 in rabbit). Coefficients for most tissues were lower and similar between species. One notable exception was blood (coefficients of 39 in rat, 12 and 16 in rabbit fetus and doe, and 18 and 17 in human males and females, respectively). Another exception was thyroid: coefficients were 11 and 39 for rat and rabbit, respectively. These partitioning data have limitations in their usefulness, since they represent non-living, non-perfused tissues. Supplementary data. Aldous, 4/15/05.

52875–0072 215240 Earlier draft submission related to 52875–0079 216073.

52875-0080 216075 Himmelstein, M. W., “In vivo 2-day inhalation mechanistic toxicity study in the rat,” E. I. du Pont de Nemours and Co., Haskell Laboratory for Health and Environmental Sciences, Newark, DE; Exygen Research, State College, PA; and University of Massachusetts Medical School, Worcester, MA. Final Report Date: 12/16/04. Laboratory Study #: DuPont-14998. Male Sprague-Dawley rats/group were exposed whole-body to 0, 25, or 100 ppm of Iodomethane Technical (Lot No. 305515 (Haskell Lab No. H-26418), purity: 99.85%, and Haskell Lab No. H22703-303, purity: 99.98%). Two 6-hour exposures were performed on consecutive days. From 1 to 48 hours after the initiation of the first exposure, 3 animals/group/time point (namely 1, 3, 6, 9, 24, 25, 27, 30, 33, and 48 hr after initiation) were euthanized. These rats were sampled for glutathione levels (GSH) in the blood, liver, kidneys, and nasal olfactory and nasal respiratory epithelium. In addition, serum iodide was measured in these groups. An additional 10 animals/group (same dose levels) were euthanized at 48 hours post-study initiation, and hematology, clinical chemistry (including thyroid-associated hormone assays), hemoglobin adduct assays, and liver UDP-glucuronyltransferase (UDPGT) activity analyses were performed. An adjunct study was performed in which 4 males/group were exposed to the test material at the same concentrations for one 6-hour exposure period. The pulmonary function of these animals was evaluated over the course of the exposure. Additional serum iodide and hemoglobin adduct level values were determined at the conclusion of that exposure. No deaths resulted from any
exposures. Maximal GSH changes in 100 ppm rats were about 40% decrements in blood, liver, and kidneys; whereas about 80-85% decrements occurred in nasal olfactory and nasal respiratory epithelium. Maximal GSH decrements in 25 ppm rats were also large, particularly in nasal epithelia (40-50% maximal decrements). GSH decrements demonstrated an exposure-related time course during both of the exposure periods, with recovery to pre-exposure levels prior to the initiation of the second exposure. Depletion of the GSH levels in nasal epithelia was less apparent during the 2nd day of exposure than on the initial exposure, suggesting compensatory response. Serum iodide concentrations of 25 ppm rats were elevated about 1000-fold over controls, with concentrations in 100 ppm groups an additional 2- to 4-fold higher. Serum iodide concentrations typically fell to less than 10% of peak levels after 18 hr of recovery. There was no treatment-related effect upon the hematology parameters. In the clinical chemistry evaluation, serum cholesterol, and high- and low-density lipoproteins were increased in an exposure-related manner (p<0.05). Serum triglycerides were decreased in an exposure-related manner (p<0.05). TSH was increased in an exposure-related manner (p<0.05), whereas serum T3 and T4 levels were decreased for the 100 ppm group (p<0.05). UDPGT activity was unchanged, suggesting that thyroid hormone reductions were not due to enhanced metabolism of T4. Methylcysteine globin adducts were increased in an exposure-related manner (approximately doubled and statistically significant (p<0.01) at 100 ppm). There was no apparent treatment-related effect upon the pulmonary function parameters, however these assessments were not sensitive due to large variations and small sample sizes. Study supplemental. (Moore and Aldous, 3/24/05).

52875-0071 215236 (earlier submission of 52875-0080 216075, above). No worksheet.
52875-0071 215236 (earlier submission of Appendix H of 52875-0080 216075, above). No worksheet.

52875-0106 224026 Chamberlain, M. P., E. A. Lock, B. A. Gaskell, and C. J. Reed, “The role of glutathione S-transferase and cytochrome P450-dependent metabolism in the olfactory toxicity of methyl iodide in the rat,” Arch. Toxicol. 72: 420-428 (1998). Techniques and findings from this study contributed to the design of the Himmelstein study (52875-0080 216075, above). Investigators dosed groups of 5 Alpk:APfsD rats for up to 6 hr at 0 or 100 ppm MeI. Primary observed outcomes were (1) decrements in “non-protein sulfhydryl” groups [abbreviated NP-SH, of which glutathione (GSH) is the prototype] in olfactory and respiratory epithelium and in other tissues, and (2) extent of destruction of olfactory epithelium. Respiratory epithelium, noted to receive about 80% of the nasal air flow, showed NP-SH depletion to about 45% of control levels after 15 min of MeI exposure, and was below limits of detection after 2 hr. Olfactory epithelium and lung NP-SH depletion fell to about 40% of controls by 1 hr, and NP-SH subsequently fell minimally thereafter in these tissues. Degeneration of olfactory epithelium was prominent at 2 hr, and greatly increased after 4 hr of treatment. Rats administered the isopropyl ester of GSH prior to MeI exposure had substantially lessened the extent of pathology in the olfactory epithelium compared to rats without such protection. Investigators pre-treated some groups with cobalt protoporphyrin IX (which depleted cytochrome P450 activities by about 85% in liver in this study, and which has been shown elsewhere to deplete P450 in other tissues). Such treatment did not demonstrably affect the degree of olfactory epithelium pathology caused by MeI inhalation. Key findings in this study were that (1) it appears that respiratory epithelial toxicity due to MeI is associated with GSH depletion rather than to products of GSH metabolism, and (2) depletion of cytochrome P450 stores in (at least) olfactory epithelium is not a large contributory factor to pathology. [Note that the Himmelstein study cited in this paragraph also evaluated MeI effects on respiratory and olfactory epithelia, and provided dose-response over the range of 25 to 100 ppm.] Aldous, no worksheet for this publication, 3/6/07.
Farwell, A. P., “Effect of TM-425 (methyl iodide) on deiodinase activity,” Molecular Endocrinology Laboratory, Univ. of Massachusetts Medical School, Worcester, MA, 12/21/04. Laboratory Study #: Deiodinase 1234. This report presents only highly reduced data (plots and histograms), hence cannot be independently validated. **Methods:** The investigator evaluated effects of iodomethane on deiodinases, which remove iodine moieties from thyroid hormones, T3 and T4, in various tissues, as follows: [1] Type I 5'-deiodinase (D1) removes an iodine from the outer ring, and is found mainly in liver, kidney, thyroid, and brain, [2] Type II 5'-deiodinase (D2) also removes an iodine from the outer ring, and is found mainly in brain, pituitary, and rodent brown adipose tissue, [3] Type III 5'-deiodinase (D3) removes an iodine from the inner ring, and is found mainly in placenta and brain. Types D1 and D2 deiodinases were evaluated *in vitro* and *in vivo*, whereas D3 was evaluated only *in vivo*. Although not specified in the report, it appears that $^{125}$I was incorporated into commercially-available rT3-$^{125}$I for use in D1 and D2 assays, which used an “iodide release method” for analyses. D3 was assayed following HPLC separation by an unspecified detection method. *In vitro* studies used (1) liver and kidney tissues from “adult euthyroid rats” [sex(es) and strain not specified] for D1 assays, and (2) astrocyte cultures prepared from neonatal rats for D2 assays. *In vivo* studies used tissues set aside from other studies reviewed separately by DPR. The supplementary rabbit toxicity “mode of action” study (Sloter, E. D., DPR Document No. 52875-0086, Record No. 216255, Laboratory Study #: WIL-418032) provided tissues from does and fetuses. Tissues were collected immediately after the fourth of 4 daily 6-hr exposures (gestation day 26). Tissues were provided from five does/group, and one fetus of each of those does. That study provided maternal and fetal liver and kidney samples used in the present D1 assays, brain samples from does and fetuses for the D2 assays, and placentas for the D3 assay. The 2-day inhalation mechanistic rat study (Himmelstein, M. W., DPR Document No. 52875-0080, Record No. 216075, Study # DuPont-14998) provided tissues from the dams, killed 18 hr after the second day’s exposure (5 dams/group). No deiodinase assays were performed on fetal tissues from the rat study. The liver and kidney tissues from the rat study were used in the present D1 assays, and brains from that study were used for the present D2 and D3 assays. **Results:** *In vitro* assessments for D1 (in rat liver and rat kidney microsomes) showed reduced activities at 25 to 50 mM (apparent NOEL of 10 mM). Both tissues yielded non-linear Dixon plots (indicative of non-competitive inhibition: probably enzyme inactivation). Further evidence of enzyme inactivation was that preparations incubated with concentrations iodomethane sufficient to reduce deiodinase activity did not regain activity when subsequently diluted below apparently toxic concentrations. When rat-derived astrocyte cultures were treated with iodomethane, D2 activity was inhibited at and above 1 mM, however concentrations of 1 mM and possibly even 0.1 mM were cytotoxic under these conditions, based on dye exclusion properties. D2 activity in astrocyte lysates was inhibited at about 5 mM and above. Dixon plot and dilution-recovery studies (similar to D1 tests, above) were also consistent with enzyme inactivation. *In vivo* tests in rats dosed with 0, 25 or 100 ppm iodomethane (Himmelstein study) showed reduced activities at 25 to 50 mM (apparent NOEL of 10 mM). Both tissues yielded non-linear Dixon plots (indicative of non-competitive inhibition: probably enzyme inactivation). Further evidence of enzyme inactivation was that preparations incubated with concentrations iodomethane sufficient to reduce deiodinase activity did not regain activity when subsequently diluted below apparently toxic concentrations. When rat-derived astrocyte cultures were treated with iodomethane, D2 activity was inhibited at and above 1 mM, however concentrations of 1 mM and possibly even 0.1 mM were cytotoxic under these conditions, based on dye exclusion properties. D2 activity in astrocyte lysates was inhibited at about 5 mM and above. Dixon plot and dilution-recovery studies (similar to D1 tests, above) were also consistent with enzyme inactivation. *In vivo* tests in pregnant rabbits exposed to 20 ppm (the only treated group assessed in the above-cited Sloter study) showed kidney D1 activity reduced by about 65% compared to controls. Livers from the same does showed no treatment response. Fetuses had no treatment changes in D1 activity for either organ. Brain D2 activities were unchanged by 20 ppm iodomethane in rabbit does or fetuses. D3 activity in the placenta were also unaltered by treatment. The latter *in vivo* rabbit assessments also included NaI treatments (4 consecutive days by iv infusion, at the rate of 81.2 μmol/doe per 6-hr treatment period). NaI did not effect maternal or fetal parameters assessed in this study. These results
collectively give equivocal indications of deiodinase activity inhibition in adults (poor correlation between \textit{in vivo} kidney and liver responses, which share the same (D1) deiodinase type). Also, \textit{in vivo} tests evaluated too few dose levels to provide a possible dose-response for D1 deiodinase effects. Results indicate that it is unlikely that deiodinase inhibition was a factor in rabbit developmental toxicity studies. Supplementary study, not applicable to data requirements. There are no individual data to verify the summary data of the investigator. The study parameters and methodologies are uncommonly used in support of pesticide registrations. Methodologies are not validated for regulatory purposes. It is thus difficult to judge the importance of stated findings except by comparison to concurrent controls. It is unlikely that important new conclusions would be obtained with additional clarifications of present data, however additional \textit{in vivo} studies on D1 deiodinase in rabbit kidney and liver may be useful. Aldous, 6/13/05.

52875--0072 215242 Draft without a date, probably related to 52875--0084 216253, above. No DPR review.

52875--0079 216074 DeLorme, M. P., “Iodomethane: pulmonary function study in the rabbit,” E. I. DuPont de Nemours and Company, Newark, DE, 12/16/04. Laboratory Study #: DuPont-15453. Four NZW rabbits/group received a single treatment with 0 or 18.5 ppm iodomethane (99.7% purity) in non-restraining plethysmographs for 6 hr. Breathing rate, tidal volume, and minute volume were measured or calculated during exposure. Immediately following exposure, blood was sampled for analysis of inorganic serum iodide and hemoglobin adducts (as S-methylcysteine from the isolated globin fraction: methodology similar to that of Record No. 216255). Mean breathing frequency did not vary with treatment (131 and 127 breaths/min in controls and treated rabbits, respectively). Tidal volume and therefore minute volume were remarkably elevated in treated rabbits (mean tidal volume of 3.7 and 5.1 ml, and minute volume of 404 and 524 ml/min, respectively). There were non-significant elevations of S-methylcysteine concentrations in rabbit globin from RBC lysates of treated rabbits (mean ± SD of 70 ± 3 in controls vs. 89 ± 20 in treated animals). The latter is suggestive but not definitive evidence of an increase over background methylation. Major elevations in serum iodide were obtained with treatment: 9 ng/ml in controls vs. 11,800 ng/ml in treated rabbits. Treatment did not elicit clinical signs. Useful supplementary data. Aldous, 4/18/05.

52875-0072 215239 earlier draft of 52875--0079 216074 (no DPR review).

**SUBCHRONIC**

**90-Day Rat Inhalation Toxicity Study**

**52875-017 185692, “A 13-Week Inhalation Toxicity Study (with a Four-Week Interim Necropsy) of Iodomethane in Albino Rats” (Daniel T. Kirkpatrick, WIL Research Laboratories, Inc., Ashland, OH., Report # WIL-418015, 28 January 2002).** 20 Crl:CD*(SD)IGS BR rats per sex per group received whole-body inhalation exposure to iodomethane technical (99.7% purity) at 0 (filtered air), 5, 20, and 70 ppm for 6 hours per day, 5 days/week. Mg/m³ equivalent exposure concentrations were 28, 113, and 396 mg/m³ at 5, 20, and 70 ppm respectively. 10 per sex per group were necropsied after 4 weeks, the remaining animals were treated through week 13. Higher mean relative (to bodyweight) liver weights (15% and 22% for males and females respectively relative to controls) at 70 ppm were observed at week 13. Cumulative bodyweight gains for weeks 0 through 13 were decreased 15% and 17% for males and females respectively at 70 ppm. Gains were decreased < 10% at 5 and 20 ppm for males. Degeneration/regeneration of the olfactory epithelium was noted for both sexes at 70 ppm at weeks 4 and 13. NOAEL = 20 ppm (113 mg/m³). \textbf{Acceptable.} (Green and Gee, 6/12/02).
This segment of the report is a range-finding study to set dose levels for the subchronic study, Record No. 185692, above. Time frame of the in-life phase of this study was Feb. to March, 2001. This study used iodomethane dose levels of 0, 25, 75, and 100 ppm for 6 hours per day, 5 days/week, for 4 weeks. There was some depression of body weight gains and of food consumption in males at 75 and 100 ppm, and of body weight gains in females at 75 and 100 ppm. There were some hematology and clinical chemistry changes possibly due to treatment at these levels. Histopathology was assessed only in controls and high dose rats. Common histopathology effects in both sexes at 100 ppm included hypertrophy of the pars distalis of the pituitary, degeneration of nasal epithelium, and thyroid hyperplasia and degeneration. Dose levels selected for the primary subchronic study were appropriate, based on this range-finding study. This 4-week study is unsuitable for setting NOEL’s due to the limitations of study design. No DPR worksheet is needed. Aldous, 4/9/07.

**Nishimura, Y, “A 90-day repeated oral dose toxicity study of iodomethane in rats followed by a 28-day recovery (with amendments),” Shin Nippon Biomedical Laboratories, Ltd., 2/18/02. Laboratory Study #: SBL98-24. Groups of 10 Crj: SD (SD) IGS rats/sex/group were dosed daily by gavage to 0, 5, 10, 25, or 50 mg/kg/day of Iodomethane Tech. in corn oil, 99.9% purity, for 13 weeks in a standard subchronic study. Additional groups of 10/sex were dosed at 0, 25, or 50 mg/kg/day, then kept off treatment for 4 weeks prior to sacrifice to evaluate recovery. Clinical signs taken within 2 hr of daily dosing found salivation in nearly all 25 and 50 mg/kg/day rats, and in about half of 10 mg/kg/day rats. This sign was not observed longer than 2 hr after daily dosing, thus should be considered as a repeated acute or subacute response, rather than as a subchronic endpoint. Subchronic NOEL = 5 mg/kg/day, based on hyperkeratosis and hyperplasia in the forestomach (LOEL of 10 mg/kg/day in males, and 25 mg/kg/day in females), and submandibular gland ductal squamous metaplasia (LOEL of 10 mg/kg/day in both sexes). Submucosal edema of glandular stomach submucosa was observed in two surviving 50 mg/kg/day females. Hepatocytic focal necrosis was observed in 4/10 males at 50 mg/kg/day, and in 1/7 surviving females at that dose: this finding in males indicating a plausible treatment response. Study is acceptable. Reactions in above epithelial tissues are “possible adverse effects.” Aldous, 5/10/07.

Rat 21-Day Dermal Toxicity Study

**Morris, T. D., “A repeated-dose 21-day dermal toxicity study of iodomethane in rats,” WIL Research Laboratories, Inc., Ashland, 1/22/02. Laboratory Study: WIL-418009. Ten Crl:CD®(SD)IGS BR rats/sex/group were dosed with iodomethane (99.7%) applied in corn oil (2 ml/kg) to clipped intact mid-dorsal skin, the site then being covered with gauze and taped in place with plastic wrap for 6 hr/day over 21 consecutive days. NOEL for test site is below 30 mg/kg/day (lowest dose tested), based on erythema and mild exfoliation (non-statistically significant in 2-way comparisons, but qualitatively related to effects at higher dose levels). Systemic NOEL (other than application site) = 30 mg/kg/day, based on significant body weight and food consumption decrements in males, significant decreases in RBC parameters in both sexes, with compensatory increase in platelets (significant in males), altered leukocyte counts (significantly increased neutrophils and decreased lymphocytes in both sexes), sharp decreases in albumin and elevations of globulin in both sexes, elevated BUN in both sexes without evident kidney toxicity in survivors (although urinary tract obstruction was considered to be cause of death in 3 of the 4 male decedents), significantly elevated alkaline phosphatase in both sexes, and significantly elevated ALT and AST in females (without remarkable liver histopathology except for elevated “minimal” grade extramedullary hematopoiesis in females), other indications of hematological change including significantly elevated lymphoid necrosis of the thymus in both sexes, extramedullary hematopoiesis in spleen (significant in both higher dose groups of females
and in 1000 mg/kg/day males), and generally significant elevation of hypercellularity in sternal marrow. Acceptable, with local tissue reactions as “possible adverse effects.” Aldous, 5/10/07.

**Mouse 3-Week Dietary Toxicity Study**

52875-0043; 202614; “A 21-Day Dietary Range-Finding Study of Microencapsulated Iodomethane in Mice”; (J.F. Harriman; WIL Research Laboratories, Inc., Ashland, OH; Study No. WIL-418020; 1/21/03); Ten Crl:CD-1 (ICR)BR mice/sex/group received 0, 62.5, 250 or 1000 ppm of Microencapsulated Iodomethane (SWRI Sample 20-312; a.i.: 2.2%) in the diet for 3 weeks (21 or 22 days) ((M) 0, 11.3, 43.2, 154.0 mg/kg/day, (F) 0, 13.5, 53.1, 168.0 mg/kg/day). No deaths occurred during the study. The mean body weights for the 1000 ppm males and females were less than that of the controls over the course of the study (p<0.01). Mean body weight gain for the 250 (p<0.05) and 1000 ppm males and the 1000 ppm females (p<0.01) during the first week of the study was less than that of the controls. Mean food consumption of the 1000 ppm group was lower than that of the control (p<0.01). In the necropsy examination, the mean absolute kidney, heart, and spleen weights of the 1000 ppm males and females and the mean ovarian weight of these females were less than those of the controls (p<0.01 or p<0.05). However, the relative mean weights of these organs were not significantly affected. The relative mean weights of the brain for both sexes in the 1000 ppm group were greater than those of the control (p<0.01). **No adverse effect indicated.** Reported NOEL: 62.5 ppm (based upon reduced body weight gain of the 250 ppm males). **Study supplemental** (non-guideline study) (Moore, 3/19/03)

**Mouse 90-Day Dietary Toxicity Study**

52875-0049; 205499; “A 90-Day Dietary Toxicity Study of Microencapsulated Iodomethane in Mice”; (J.F. Harriman; WIL Research Laboratories, Inc., Ashland, OH; Study No. WIL-418021; 5/6/03); Ten Crl:CD-1 (ICR)BR rats/sex/group received in the diet 0, 133, 400 or 1200 ppm of Microencapsulated Iodomethane (SWRI Sample nos. 20-338, 20-340; a.i.: (20-338) 2.32 to 3.13%, (20-340) 3.71 to 3.81%) for 13 weeks ((M) 0, 23.6, 65.3, 212.0 mg/kg/day, (F) 26.8, 79.2, 221.6 mg/kg/day). One male and one female in the 1200 ppm group died on days 60 and 7, respectively. The mean body weight gain of both sexes in the 1200 ppm was reduced during the first week of the study with no apparent treatment effect thereafter (p<0.01). Mean food consumption was likewise affected during the first week for the 1200 ppm group, indicating a possible palatability problem. The high dose animals demonstrated an increased incidence of decreased defecation ((M) 0: 0 vs. 1200: 22 times for 6 animals, (F) 0:0 vs. 1200: 25 times for 7 animals). No treatment-related effects were noted in the hematology, clinical chemistry, ophthalmology and urinalysis. In the necropsy examination, the mean absolute kidney weight for the 1200 ppm males and the mean absolute adrenal and ovary weights for the 1200 ppm females were less than those of the control (p<0.05 or 0.01). However, the mean relative weights for these organs were not statistically different from those of the control. The mean absolute and relative thyroid weights for the males in the 133 ppm group and above were greater than those of the control (p<0.05 or 0.01). The mean absolute and relative thyroid weights for the females in the treatment groups were greater than the control but the differences were not statistically significant. In the histopathology examination, there was an increased incidence of increased colloid in the thyroid glands of both sexes in all of the treatment groups ((M) 0: 1/9, 133: 8/10, 400: 9/10, 1200: 8/9, (F) 0: 1/10, 133: 9/10, 400: 9/10, 1200: 9/9). The incidence of hyperkeratosis in the esophagus was increased in a dose-related manner for both sexes ((M) 0: 0/10, 133: 1/10, 400: 7/10, 1200: 9/9, (F) 0: 0/10, 133: 2/10, 400: 7/10, 1200: 7/9). Myeloid hyperplasia was noted in the bone marrow of the femur in the 1200 ppm females (0: 0/10 vs. 1200: 2/9). An increased incidence of porphyrin pigment in the Harderian gland of the 1200 ppm females was noted as well (0: 1/10 vs. 1200: 5/9). **Possible adverse effect:** increased incidence of increased colloid in the thyroid gland. **Subchronic NOEL:** (M/F) < 133 ppm ((M) 23.6 mg/kg/day, (F) 26.8 mg/kg/day) (based upon the increased
incidence of colloid in the thyroid gland and the incidence of hyperkeratosis in the esophagus of the 133 ppm treatment group); **Study acceptable.** (Moore, 8/28/03)

**Dog 3-Week Oral Toxicity Study**

52875-0037; 200879; “A 3-Week Capsule Dose Range-Finding Study of Iodomethane in Dogs”; (J.W.M. Mertens; WIL Research Laboratories, Inc., Ashland, OH; Study No. WIL-418016; 8/29/02); Two groups of 2 beagle dogs/sex/group were dosed with Iodomethane (batch: 2, lot no. 007403, purity: 99.7%) in capsules according to the following regimen: 5 days at 3 mg/kg/day, 2 days of non-dosing, 2 days at 30 mg/kg/day, one day of non-dosing, 1 day of 15 mg/kg, 5 days of non-dosing and 5 days of 7.5 mg/kg/day. Group I was dosed after being fed for 2 hours. For Group II, food was provided *ad libitum* 3 hours after dosing until the time of dosing the next day. No deaths resulted from the treatment. Treatment-related effects for the 15 mg/kg treatment could not be determined due to the brevity of the treatment. At 30 mg/kg/day, body weight and food consumption decreased for 6 of 8 animals with all of the animals in Group I being affected. Emesis and decreased defecation were noted for this treatment. Clinical signs resulting from the 7.5 mg/kg/day treatment were infrequent occurrence of emesis, mucoid feces containing red material and injected sclera. Injected sclera was noted for some animals in the 3 mg/kg/day treatment group. No treatment-related lesions were noted in the necropsy examination. **No adverse effect indicated.** NOEL not established due to the use of different dosing regimens for different time periods. **Study supplemental.** (Moore, 12/3/02)

**Dog 90-Day Oral Toxicity Study**

52875-0040; 201696; “A 90-Day Oral (Capsule) Toxicity Study of Iodomethane in Dogs”; (J.F. Harriman; WIL Research Laboratories, Inc., Ashland, OH; Study No. WIL-418017; 10/17/02); Four beagle dogs/sex/group were dosed orally with 0, 1.5, 6.0 or 15.0 mg/kg/day of Iodomethane (TM-425) (lot no. 007403, batch no. 02, purity: 99.7%) in capsules for 90 days, 7 days/week. One male in the 15.0 mg/kg treatment group was euthanized *in extremis* on day 48, exhibiting signs of emaciation, emesis, dehydration and limited food consumption. For the survivors, there was no treatment-related effect upon body weight or food consumption. Clinical signs included moderately to markedly injected sclera of the eye ((M) 1.5 mg/kg and above, (F) 6.0 mg/kg and above), drooling and wet material around mouth ((M) 1.5 mg/kg and above, (F) 6.0 mg/kg and above), emesis ((M/F) 15.0 mg/kg) and head shaking ((M/F) 15.0 mg/kg). There were no treatment-related effects upon the hematology or urinalysis. The mean albumin serum concentrations of the 15.0 mg/kg males and females at 6 and 12 weeks and the 6.0 mg/kg females at 12 weeks were less than those of the controls (p<0.05 or 0.01). The total protein concentrations in the serum were likewise affected in these groups. There was no treatment-related effect upon organ weights. In the histopathological evaluation, an increased incidence of minimal degeneration of the olfactory epithelium was noted in the nasal level IV section of the 6.0 and 15.0 mg/kg females (0: 1/4, 1.5: 1/4, 6.0: 3/4, 15.0: 3/4). However, this effect was not evident in the males and appeared to be incidental to the increased incidence of emesis in these animals. **Possible adverse effect:** possible neurological involvement (head shaking); **NOEL:** (M) < 1.5 mg/kg/day (based upon increased incidence of markedly injected sclera of the eye and salivation for 1.5 mg/kg treatment group), (F) 1.5 mg/kg/day (based upon increased incidence of markedly injected sclera of the eye and salivation for 6.0 mg/kg treatment group); **Study acceptable.** (Moore, 12/4/02)
Supplemental Data (Many of these records are relevant for risk assessment.)

52875-0101 219525 Gargas, M. L., L. M. Sweeney, and C. R. Kirman, “Weight of evidence for evaluation of the HEC for acute developmental toxicity of methyl iodide,” The Sapphire Group, Inc., Dayton, OH, July 8, 2005. This record reiterates the human-equivalent no-effect concentration (HEC) for potential developmental effects of acute exposure to Mel to be 17 ppm, based on the evidence that (1) iodide is the ultimate metabolite response for fetal effects, (2) that human fetuses do not accumulate iodide, whereas rabbit fetuses do, (3) that there is adequate information to characterize human and rabbit maternal and fetal models of iodide disposition. The present record includes some tables of sensitivity coefficients, which address uncertainties of the model values. The HEC of 17 ppm presented here had been proposed previously, particularly in DPR Document No. 52875-0096, Record No. 218692: Sweeney, L. M., and M. L. Gargas (Project No. 34503, 4/29/05: see below). The present record cites an article which does not appear to have been submitted to DPR, which may have the actual formula which yielded this HEC: [Sweeney, L. M., C. R. Kirman, and M. L. Gargas, (2005). Derivation of human toxicity reference values for methyl iodide using physiologically based pharmacokinetic (PBPK) modeling. The Sapphire Group, January 13, 2005]. That article is requested. Many supportive published articles are appended to this record. No DPR worksheet. Aldous, Aug. 9, 2005.

This is the only DPR summary from volume entitled “Weight of evidence for evaluation of the HEC for acute developmental toxicity of methyl iodide.”

52875-0104 219538 Sweeney, L. M. and M. L. Gargas, “Reevaluation of the HEC for acute nasal toxicity of methyl iodide” (Supplemental to MRID No. 46446901). Authors propose an HEC of 5.8 from rats to humans. Record includes numerous supportive published articles. No DPR worksheet. Aldous, 9/9/05.

52875-0103 219528 [Memorandum] McDonald, T. A. “Evaluation of information submitted to U.S. EPA on behalf of Arysta LifeScience North America Corporation related to the assessment of the chronic exposures of iodomethane, a preplant soil fumigant,” Aug. 1, 2005. This 7-page memo proposes that thyroid effects including tumors in laboratory animals are unlikely to lead to thyroid tumors in humans at dose levels that are not acutely toxic. No DPR worksheet. Aldous, 9/9/05.


52875–0053 209160 “Audited Draft” of the report reviewed and accepted in final form under 52875–0058 209863. No DPR review is relevant for this draft. Aldous, 4/18/05.

52875–0057 209861 Amendment to subchronic study: [52875-0049; 205499; “ A 90-Day Dietary Toxicity Study of Microencapsulated Iodomethane in Mice”; (J. F. Harriman; WIL Research Laboratories, Inc., Ashland, OH; Study No. WIL–418021; 5/6/03]. This amendment was examined by Moore on 3/22/04, and found not to affect DPR conclusions. No worksheet was generated for this amendment by DPR.

52875-0059 209864 Exact duplicate of 52875-0044 202615 (previously reviewed by DPR).

52875-0059 209865 Exact duplicate of 52875-0044 202616 (previously reviewed by DPR).
52875-0095  217700  Miles, B. E., L. Sweeney, and C. Kirman, “Risk assessment of thyroid follicular cell tumors in rats following 2-year iodomethane exposure by inhalation.” Technology Sciences Group, Inc., Washington, DC, Project ID 810-03, 3/30/05. This report discusses the rat inhalation combined study (see Document No. 52875-0094) and presents various published articles on thyroid function, toxic perturbations of the thyroid, and toxicity issues of iodomethane and other halomethanes. This volume does not report new studies, and there is no worksheet from the DPR data review groups. Aldous, 5/6/05.

52875-014 185684  Burin, G. J. and B. E. Mileson, 1/25/02. A synopsis of FIFRA studies supporting iodomethane, plus a collection of published studies, reviews, and abstracts on iodomethane. No new FIFRA studies are in this volume, and no DPR data review worksheet is needed at this time. Aldous, 5/6/05.

52875-0105 224020  U.S. EPA DER’s for product chemistry, environmental fate, fish and wildlife, risk assessment and toxicity.

52875-0060 213146  This volume, dated 8/14/04, contains four protocols for upcoming MeI studies, 8 progress reports for MeI studies, and published reports of 7 PBPK studies on materials other than MeI. No DPR Data Review Group worksheet is appropriate. Aldous, 3/5/07.

52875-0062 213737  This volume, with cover letter of 9/3/04, contains primarily progress report and protocols. No DPR Data Review Group worksheet is appropriate. Aldous, 3/5/07.


52875-0106 224021, 224022, 224023, 224024, 224025, 224027, 224028, 224029, 224030, 224031, 224032. This volume contains primarily journal articles on iodide effects in human pregnancies and animal studies. The above listed records are not considered by the DPR Data Review Group to warrant worksheets. Record 224026 was, however, is described in this Summary. Aldous, 3/6/07.

52875-0107 224032, 224033, 224034, 224035, 224036, 224037, 224038, 224039, 224040, and 224041. This volume contains primarily journal articles on iodide effects in human pregnancies and animal studies. The listed records are not considered by the DPR Data Review Group to warrant worksheets. Aldous, 3/6/07.

52875-0108 224042, 224043, 224044, 224045, and 224046. This volume contains primarily journal articles related to thyroid function and toxicity to epithelia of the respiratory system. Record No. 224046 is entitled: “Assessment of thyroid follicular cell tumors.” Many of these records may be useful for risk assessment. The listed records are not considered by the DPR Data Review Group to warrant worksheets. Aldous, 3/6/07.

52875-0109 224248 This record was provided primarily to support registrants’ concerns relating to risk assessment issues. The record is not suitable for a DPR Data Review Group worksheet. Aldous, 3/6/07.

52875-0110 228415 This analysis relating to nasal epithelial pathology due to MeI, including supporting publications, was presented to aid DPR risk assessment. No DPR Data Review Group worksheet. Aldous, 3/6/07.
52875-0115  228420  Mézin, L. “Abstracts and tables for three studies on the effects of iodomethane on biological functions in mice, rats and dogs,” 8/23/06. Translations of abstracts and selected tables for 3 non-FIFRA studies conducted at Shin Nippon Biomedical Laboratories, Ltd. MRID 46934304. Only minimal information from the studies was reported.

1. Biological function in mice. Mice were administered single doses of iodomethane in corn oil at 0, 12.5, 25, 50, 100, or 200 mg/kg. Mice were observed for physical condition and behavior. Charcoal meal (7.5%) was administered 30 min after dosing to assess intestinal transport and stomach emptying, apparently by longitudinal sectioning at necropsy. The appearance and behavioral NOEL = 50 mg/kg. Findings at 100 mg/kg included sedation, prone position, body shaking, and drooping eyelids: all of these mice survived, and most signs did not persist past 8 hr. All 200 mg/kg mice died within 2 hr, with the above symptoms plus abnormal gait and other agonal changes. Intestinal transport was normal at 12.5 mg/kg, significantly retarded at 25 to 50 mg/kg, and again normal at 100 mg/kg. Investigators considered the findings at 25 to 50 as treatment-related, making the NOEL = 12.5 mg/kg for intestinal transport. Supplementary data.

2. Biological function in rats. Rats were administered single doses of iodomethane in corn oil at 0, 12.5, 25, 50, or 100 mg/kg (N = 8). Investigators recorded blood volume and concentrations of Na+, K+, and Cl-. There was a statistically significant increase in concentration of urinary Na+ at 100 mg/kg. There were no other significantly significant changes in electrolytes, nor in urinary volume. Investigators considered non-statistically significant increases in K+ and Cl- concentrations at 25 mg/kg to be biologically significant. Results were sufficiently variable and sufficiently lacking in meaningful trends, that this DPR reviewer finds no actionable values below 100 mg/kg. Supplementary data.

3. Biological function in Dogs. Male beagles (N = 3) were administered single doses of iodomethane once “intra-duodenally” prior to assessing respiratory rate; arterial blood measures of pH, oxygen tension (PaO2), CO2 tension (PaCO2); hemoglobin oxygen saturation (SaO2); blood pressure, heart rate, and EKG. Dose levels were 0, 15, 30, and 60 mg/kg. Investigators considered there to be a meaningful increase in respiratory rate and a meaningful decrease in PaCO2 at 30 and 60 mg/kg. Respiratory rate pre-test values varied 6-fold between dogs, so that this was unlikely to be a sensitive test. At least one dog in each group had a low breathing rate (4-7 breaths/min), and none of these dogs had altered breathing rates attributable to treatment. Since one 30 mg/kg dog had a nearly 2-fold increase in breathing over its pre-treatment condition, and since one 60 mg/kg dog attained a breathing rate of 32-33 breaths/min after 30-60 min (well above its own or any other pre-treatment breathing rate in dogs on study), a treatment effect at 30 mg/kg is possible and very likely at 60 mg/kg. It appears that there was a dose-related decrease for PaCO2 at 30-60 mg/kg. Thus the NOEL proposed by investigators for these respiratory parameters (15 mg/kg) is supportable. Supplementary data.

Overall conclusion by DPR reviewer. These three studies were very limited in scope, sparingly reported, and did not appear to reveal findings of unique safety concern. There is no reason to pursue further information from these studies. No DPR worksheets. Aldous, 4/18/07.