Predictions for the Outcome of Rodent Carcinogenicity Bioassays: Identification of Trans-species Carcinogens and Noncarcinogens

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Thirty chemicals or substances currently undergoing long-term carcinogenicity bioassays in rodents have been used in a project to further evaluate methods and information that may have the capability of predicting potential carcinogens. In our predictions the principal information used includes structural alerts and in vitro test results for Salmonella mutagenicity, relative subchronic toxicity, and the sites and types of pathology found in subchronic (90-day) studies. This group of chemicals differs significantly from those used previously to evaluate predictive methods in that 23 of 30 are defined as nonmutagenic by conventional criteria. The goal of this predictive effort is to identify categorically the chemicals that have the capacity to induce cancers in both rats and mice (trans-species carcinogens) and those that are not carcinogenic in either rats or mice. Chemicals that show properties that may be associated with tumor induction in either species, i.e., species-specific cancers, are categorized as being of "uncertain predictability." This category includes chemicals believed to have limited carcinogenic potential that is manifested principally as a consequence of the genetic background of the test strain of inbred rodent. — Environ Health Perspect 104(Suppl 5):1095–1100 (1996)

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Introduction

An effort was initiated in 1990 to utilize ongoing rodent carcinogenicity bioassays to test the capability of using both chemical and biological parameters to predict potential carcinogens (1). It was anticipated that this would be an iterative process in which insights and knowledge gained in the first phase would be utilized to improve subsequent prediction capability. In the first phase of the project 44 chemicals undergoing rodent bioassays by the U.S. National Toxicology Program (NTP) were utilized as the target and our predictions were published to encourage the application of predictive methodologies by other investigators. Seven other prediction efforts for these chemicals were also published (2). We believe that this initial effort successfully demonstrated that the parameters of chemical structure, genotoxicity, and rodent toxicity can be used to predict potential carcinogenicity (3). Further, among the various predictive methodologies reported, the highest degree of concordance was achieved for chemicals showing the clearest carcinogenic and noncarcinogenic effects. The most problematic chemicals were those showing either sex- and species-specific or weak carcinogenic effects and those producing equivocal results.

The same biological and chemical parameters cited above and used in our previous effort (1) have been used in this second predictive exercise that involves 30 chemicals currently undergoing rodent bioassay. The principal difference in our approach to predicting the activity of this second group of chemicals is that we are demarcating more precisely the carcinogenic activity that we are attempting to predict. Extensive analysis of the results of bioassays over the past few years has provided insights into the nature of the carcinogenic responses induced in F344 rats and B6C3F1 mice, the two rodent strain/species (4,5) predominantly used in the NTP 2-year bioassay. We have proposed a stratification of bioassay results that is indicative of the relative potency of carcinogens (6). The category that reflects the greatest carcinogenic potential is that of the trans-species carcinogens that induce tumors at one or more sites in both rats and mice; a particular subcategory is represented by those that induced tumors at the same sites or of the same histogenic type in both species. The least carcinogenic potential is represented by the chemicals that induce tumors at only one site in only one of the four sex/species groups. This stratification is based on the recognition that inbred rodents possess an allelic distribution that is uncharacteristic of the type and frequency found in feral or outbred populations. That is, various alleles of polymorphic genes are represented in outbred populations with variable frequency (7). As a consequence of selected or random inbreeding, the rodent lines lose many of the polymorphic alleles and subsequently possess a more limited number of specific alleles, which are uniformly distributed in the inbred animals. Two consequences of this allelic enrichment are that the various inbred strains demonstrate specific patterns of spontaneous tumors and that they can exhibit strain-specific responses to chemicals (6–8).

Both of these consequences may be in part responsible for much of the controversy surrounding the interpretation of bioassay results and the appropriateness of their extrapolation for human risk. For example, chemicals that are identified as carcinogens based solely on increases in tumors that occur spontaneously at a high frequency (e.g., >10%), may only modulate the expression of the gene(s) that determine the disease. Since these tumors are a genetic disease of the specific rodent strain, the chemical effects may be of little consequence in other species or even other strains of the same species. The action of the trans-species carcinogens is independent of strain-specific influences and may therefore pose the greatest risk in other species, whereas the risk of the strain-specific carcinogens may affect only certain individuals in an outbred population.

The implications of the stratification of carcinogens for the prediction of carcinogenic potential is that any prediction schema must be risk-averse. That is, it must

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Abbreviations used: MTD, maximum tolerated dose; NTP, U.S. National Toxicology Program.
be possible to reliably predict trans-species carcinogens. Conversely, since the genetic and biochemical basis of strain-specific effects induced by carcinogens is not generally known, it is unlikely that they can be reliably predicted and this category of carcinogens should not be a principal basis for judging how effective prediction methods may be. A corollary to this is that the methods should also be able to reliably predict which chemicals are unlikely to induce tumors in either bioassay species.

**Results**

As in the previous exercise (1), our predictions reflect a weight-of-evidence call based on structural alerts and *Salmonella* mutagenicity data, the subchronic bioassay toxicity data, and the maximum tolerated dose (MTD) levels set for the two-year bioassay. The goal of our effort to predict the carcinogens among the 30 current chemicals is to identify all of those chemicals with trans-species carcinogenic potential and those that are noncarcinogens. In our view the data available for predicting the other chemicals cannot be reliably used to infer which may induce strain-specific tumorigenic effects; therefore all of our predictions of carcinogenicity reflect a primary concern for trans-species effects. Some data may be an alert for potential strain-specific effects, such as subchronic target-organ toxicity for tissues in which spontaneous tumors are frequent; but we have not been able to identify any reliable parameters. Likewise, we have not identified parameters of toxicity for chemicals that may induce single site/single sex/species tumors that are not associated with spontaneous tumors. This uncertainty will result in such chemicals being identified as probable noncarcinogens.

Some of the aspects of subchronic toxicity that have been identified in Table 1 have been associated with the observed strain- or species-specific responses seen in bioassays of other chemicals. They have been highlighted in the table as a possible alert to such specific carcinogenic effects even though they have no reliable predictive value. For example, hyaline droplets are often deposited in rat kidney tubular epithelium as a consequence of chronic toxicity and also have been associated with \( \alpha_2M \)-globulin related kidney tumors in male rats (9–11).

In this exercise we have identified 3 of the 30 chemicals as probable (trans-species) carcinogens, of which gallium arsenide is a nonmutagen. Ten of the 30 are predicted to be noncarcinogens. We have abstained from predicting for 2 chemicals because the outcome of the bioassay is known. This group of 30 chemicals poses a particular challenge, compared to the first exercise (1), since 23 of them are not mutagenic in the *Salmonella* assay. Though a few parameters related to the carcinogenicity of nonmutagens are known (e.g., peroxisome proliferation (11–15) and \( \alpha_2M \)-globulin hyaline droplet induced nephropathy, etc. (9–11)) none are clearly represented among this group. This is particularly important since many of the chemicals that induce strain-specific carcinogenic effects are not mutagens. Consequently, 15 of the chemicals have been classified as being of "uncertain predictability" to indicate that it is possible that strain- or species-specific neoplasia could be a consequence of chronic exposure. The above caveats may seem like a rationale for anticipated missed predictions. That is not the case because we are categorical in our efforts to predict trans-species carcinogens and noncarcinogens and the success or failure of our predictions should be judged critically on that basis.

**Discussion**

In evaluating the potential carcinogenicity of these chemicals we have again placed primary emphasis on structural alerts, mutagenicity for *Salmonella*, relative toxicity (reflected in the maximum dose tested) and the sites and type of subchronic pathology. These properties are described in Table 1, together with brief comments or explanations of the basis for our prediction. The large number of chemicals deduced to be of uncertain predictability reflects a different distribution of chemicals than those for which predictions were offered in 1990 (1). It is not anticipated that any of this group of 15 chemicals will induce trans-species carcinogenesis, but some will be associated with equivocal effects or the induction of site or species-specific carcinogenesis. A majority are anticipated to be noncarcinogens but some aspect of the subchronic toxicologic evaluation of the chemicals raises the possibility that they could be associated with site- or species-specific neoplastic effects.

It is unlikely that species- and strain-specific carcinogenicity will be predictable until the genetic basis of these occurrences is better understood. The rapid evolution in mouse genetics, in the utilization of transgenic and knockout technology to study chemical–gene interactions, and in sequencing the mouse genome to improve the identification and cloning of genes, holds the promise that specific genes and mechanisms underlying carcinogen susceptibility can be understood. We believe that at least two discrete mechanisms are involved: interaction of some chemicals with genes or gene products that modify the spontaneous tumor incidence of inbred rodents, and interactions with genes that influence tissue-specific susceptibility not associated with spontaneous tumor sites. These are potentially important issues in utilizing rodent bioassay for protecting public health and the environment. The species- or strain-specific carcinogens are unlikely to pose a public health problem that is as important as that ascribed to trans-species carcinogens. However, the genes that influence or govern species/strain specificity may be useful in identifying susceptible individual humans. To know if this is the case, it is necessary to clone such rodent susceptibility genes to determine if humans possess structural analogs. However, since cancers are the consequence of multiple genetic effects, the predominant influence of the susceptibility genes could be principally the consequence of extensive inbreeding.

We have proposed recently that specific transgenic mouse lines can be utilized in short-term carcinogenesis bioassays (8). The results available thus far suggest that the transgenic bioassays offer advantages not only in time and cost savings and a reduction in the number of animals needed for bioassays, but that they also minimize species-/strain-specific influences.
Table 1. Predictions of carcinogenicity and noncarcinogenicity for 28 chemicals undergoing the bioassay by the National Toxicology Program.*

| Chemical name                      | Route of administration | Structural alerta | Maximum dose tested in chronic bioassayb,c | Subchronic histopathologyd | Major target organs | Comments and basis for prediction |
|------------------------------------|-------------------------|-------------------|---------------------------------------------|----------------------------|---------------------|----------------------------------|
| **Probable carcinogen: trans-species effects** |                         |                   |                                             |                            |                     |                                  |
| Cobalt sulfate heptahydrate         | Inhalation              | SA– NA            | 3 mg/m³                                     | Lungs and lymph nodes, both sex/species |                     | Carcinogen: mutagen: chronic inflammation in lungs, bronchiolar epithelium regeneration; a NOEL in the lungs of rats or mice was not found. |
| Gallium arsenide                    | Inhalation              | SA– NA            | 1.0 mg/m³                                   | Lungs and larynx, both sex/species |                     | Carcinogen: nonmutagen: chronic inflammation in lungs; inorganic arsenic is a known carcinogen in humans and an enhancer of induced tumors in rats and mice; a NOEL was not reached in the subchronic rat study. |
| **Probable noncarcinogen**          |                         |                   |                                             |                            |                     |                                  |
| Cinnamaldehyde                      | Feed, microencapsulation | SA–                | Subchronic doses; 0.125, 2.5, 5.0, 10%      | Subchronic toxicity not reported out |                     | Unlikely carcinogen; nonmutagen: if high dose in the chronic study exceed 2.5% in the diet, then tumors at a sex/species specific target organ site could occur. |
| Citral                              | Feed, microencapsulation | SA–                | 2.5%                                        | Forestomach, in both sex/species; bone marrow, MR, FR; ovary, FM |                     | Unlikely carcinogen; nonmutagen: hyperplasia and hyperkeratosis of the forestomach epithelium in rats and mice, probably compound related; bone marrow atrophy and hemorrhage in rats; atrophy of ovarian corpus luteum in FM. Toxic lesions occurred at highest subchronic dose, which is 4x higher chronic study dose. (low, low risk, chronic irritation in the forestomach by a nonmutagen does not easily result in tumors). |
| Codine                              | Feed                     | SA–                | 0.16%                                       | No histopathologic lesions found in exposed rats or mice in 13-week subchronic study |                     | Unlikely carcinogen; nonmutagen: the absence of any histopathologic lesions observed in the 13-week subchronic study suggests that codeine will prove to be a noncarcinogen in the 2-year chronic study; rats exhibited poor weight gain in the subchronic study because of lowered food intake. |
| Ethylene glycol monobutyl ether     | Inhalation               | SA–                | 125 ppm                                     | Forestomach, liver, and spleen in both sex/species; bone marrow, MR, FR; kidney, MM, FM |                     | Unlikely carcinogen; nonmutagen: chronic epithelial hyperplasia of the forestomach in rats and mice induced by a nonmutagen could result in a low incidence of forestomach tumors; a NOEL was NOT reached for FM; a NOEL for hematologic effects in FR was NOT reached; most of the target organ toxicity in both sex/species occurred at highest subchronic (500 ppm) dose; a sex/species specific target organ tumor response cannot be ruled out. |
| Isobutane                           | Inhalation               | SA+                | 8000 ppm                                    | Nasal cavity, MR, FR; no histopathologic lesions in mice |                     | Unlikely carcinogen; nonmutagen: minimal hypertrophy of goblet cells lining the nasopharyngeal duct in most caudal nasal sections occurred at all doses; no NOEL observed in rats; 1,3-butadiene and chloroprene, analogs of isoprene, are carcinogens in rats and mice (NTP); high dose of isobutene in the chronic study is the same as the high subchronic dose; possible nasal passage carcinogen in rats. (continued) |
| Chemical name | Structural alert$^b$ | CAS no. | Route of administration | Structural name | Maximum dose tested in chronic bioassay$^c$ | Subchronic histopathology$^d$ | Major target organs | Comments and basis for prediction |
|---------------|----------------------|---------|--------------------------|-----------------|-----------------------------------------------|-----------------------------|----------------------|----------------------------------|
| Molybdenum trioxide$^a$ | SA-NA | 1313-27-5 | Inhalation | Anthraquinone | 100 mg/m$^3$ | 100 mg/m$^3$ | No histopathologic lesions observed in rats or mice | Unlikely carcinogen; nonmutagen: no treatment-related gross or histopathology noted, but this was an early (1984) pathology work group report; top dose in the subchronic study was chosen as the top dose in the chronic study; low, low risk. |
| Nitromethane | SA- -/− | 75-52-5 | Inhalation | Xylenesulfonic acid group | 375 ppm | 750 ppm | Nasal cavity, both sex/species; bone marrow, MR; spleen, MM, FM | Unlikely carcinogen; nonmutagen: olfactory epithelial degeneration occurred in both sex/species at subchronic doses chosen for the chronic study, analogs, tetrinitromethane (NTP) and 2-nitropropane are carcinogens in inhalation studies; rats likely are more at risk than mice. |
| Scopolamine hydrobromide trihydrate$^a$ | SA- -/− | 6533-68-2 | Gavage | Skin paint | 25 mg/kg | 25 mg/kg | No histopathologic lesions noted in rats or mice in subchronic study | Unlikely carcinogen; nonmutagen: high dose in chronic study set just above lowest dose in subchronic study because of severe reduction in secretions at higher doses; top dose is well below any expected chronic pathology. |
| Xylenesulfonic acid sodium salt$^a$ | SA- -/− | 133-72-7 | Skin paint | Xylenesulfonic acid | 240 mg/kg | 727 mg/kg | Skin in both sex/species | Unlikely carcinogen; nonmutagen: treatment-related epidermal hyperplasia not considered to lead to neoplasia; sulfonic acid group is easily detoxified via conjugation and excreted. |
| Uncertain predictability: possible sex-, species- or strain-specific target organ sites | | | | | | | | |
| Anthraquinone | SA- +/− | 84-65-1 | Feed | Anthraquinone SA- | 0.18% | 0.75% | Liver, both sex/species; thyroid, MR; kidney, MR; FR; bladder, MM, FM | Possible carcinogen; mutagen: liver hypertrophy and inflammation at all doses in rats and highest doses in mice; kidney nephropathy in MR; hyalinelike droplets in kidneys, MR and FR (thought to be parent compound); urinary bladder effects at all doses in mice. An analog, 2-aminanthraquinone, is a liver carcinogen in MR, MM, and FM; low to moderate risk. |
| t-Butylhydroquinone$^a$ | SA- -/− | 1948-33-0 | Feed | t-Butylhydroquinone SA- | 0.50% | 0.50% | Nasal lesions, both sex/species; kidney, spleen, MR, FR; skin and stomach, MM, FM | Unlikely carcinogen; nonmutagen: chronic hyperplasia of nasal respiratory epithelium in rats could lead to neoplasia; epidermal hyperplasia of the skin and epithelial hyperplasia of the forestomach in mice are unlikely to lead to neoplasia, though a spontaneous mutation in the cellular Ha-ras gene could lead to skin tumors; doses for chronic study were set at the NOEL or at a dose at which toxicity was minimal. |
| 1-Chloro-2-propanol | SA- +/− | 127-00-4 | Water | 1-Chloro-2-propanol | 0.065% | 0.10% | Pancreas, both sex/species; liver, MR | Possible carcinogen; mutagen: doses for chronic study were set at or near NOEL observed in the subchronic study in both rats and mice; low risk. |
| Diethanolamine | SA- -/− | 11-42-2 | Skin paint | Diethanolamine | 64 mg/kg MR | 32 mg/kg FR | Skin and kidney in MR, FR; skin and liver in MM, FM | Unlikely carcinogen; nonmutagen: it is unlikely that chronic skin irritation caused by a nonmutagen will result in skin neoplasia; chronic systemic effects in the rat kidney or mouse liver could lead to a specific sex or species neoplastic lesion, but the low doses selected for the chronic study may minimize that possibility; low risk. |
| 1,2-Dihydro-2,2,4-trimethylquinoline$^a$ | SA- -/− | 147-47-7 | Skin paint | Emodin | 100 mg/kg | 10 mg/kg | Skin, both sex/species; liver, MR, MM, and FM | Possible carcinogen; nonmutagen: chronic skin inflammation in both rats and mice unlikely to result in tumors; possible, but likely low risk of liver tumors in MR or in mice; low risk. |
| Emodin | SA- -/− | 518-82-1 | Feed | Emodin | 0.125% | 0.06% | Kidney, both sex/species | Possible carcinogen, mutagen: accumulation of hyalinelike droplets in the kidney thought to be emodin or a metabolite, could cause focal tubular lesions; very low risk for possible single-sex/species target organ |
### Table 1. (Continued)

| Chemical name          | Route of administration | Structural alert<sup>a</sup> | Maximum dose tested in chronic bioassay<sup>b</sup> | Subchronic histopathology<sup>c</sup> | Comments and basis for prediction |
|------------------------|-------------------------|-----------------------------|---------------------------------|---------------------------------|-----------------------------------|
| Furfuryl alcohol      | Inhalation              | SA--                        | 32 ppm 32 ppm                   | Nasal cavity, both sex/species  | Possible carcinogen; nonmutagen: chronic inflammation of olfactory epithelium, high dose in the subchronic study selected for the chronic study; an analog, furfural, was a hepatocarcinogen in MR, MM, and FM. Question of whether chronic inflammation and degeneration of the nasal epithelium, especially in rats, will lead to tumors; low risk. |
| 98-00-0                |                         | (−/+ S9)                    |                                 |                                 |                                    |
| Isobutyraldehyde      | Inhalation              | SA--                        | 2000 ppm 2000 ppm               | Nasal cavity and thymus, both sex/species; kidney, MM, FM | Possible carcinogen; nonmutagen: acute necrotizing inflammation of the nasal cavity and lymphoid depletion in spleen and thymus in both sex/species; hyperplasia of the renal tubular epithelium in mice; considered to be low risk. |
| 78-84-2                |                         | (−/+ S9)                    |                                 |                                 |                                    |
| Methyleugenol         | Gavage                  | SA--                        | 150 mg/kg 75 mg/kg             | Stomach, liver in both sex/species; kidney, adrenal and salivary gland and spleen in MR, FR; nasal cavity in MM, FM | Possible carcinogen; nonmutagen: possible liver tumors in MR, MM and FM; methyleugenol shown to be a liver tumor promoter in MM as was 1-hydroxymethyleugenol, a metabolite of ME; low to moderate risk. |
| 93-15-2                |                         | (+/−)                       |                                 |                                 |                                    |
| Oxymetholone           | Gavage                  | SA--                        | 150 mg/kg MR; 100 mg/kg FR;    | Mammary gland, adrenal gland, kidney, MR, FR; ovary and uterus, FR | Possible carcinogen; nonmutagen: dialation of the mammary gland and milk production in both MR and FR; plasmic vacuolization of adenral cortical cells, and renal tubular regeneration in MR and FR; ovarian follicular atrophy in FR; moderate risk. |
| 434-07-1               |                         | (−/+ S9)                    | chronic study in rats only      |                                 |                                    |
| Primaclone Feed        |                        | SA+/−                       | 0.25% 0.13%                    | Liver in both sex/species; kidney, MR; adrenat gland in MM | Possible carcinogen; mutagen: centrilobular hypertrophy in the liver in both sex/species; chronic kidney neophopathy in MR and cytoplasmic alteration in MM adrenal gland.10–20% of primacrine in the plasma is converted to pheno-barbitral, which is known to increase liver tumor incidence in mice and is a known liver tumor promoter in rats; low to moderate risk. |
| 125-33-7               |                         | (−/+ S9)                    |                                 |                                 |                                    |
| Pyridine               | Water                   | SA--                        | 0.04% 0.10% MM 0.05% FM        | Liver, MR, FR; kidney, MR; no histopathologic lesions in mice | Possible carcinogen; nonmutagen: hyaline degeneration in MR kidney and centrilobular degeneration in MR and FR liver; low risk for kidney tumors in MR and low risk for liver tumors in MR and FR. |
| 110-86-1               |                         | (−/+ S9)                    |                                 |                                 |                                    |
| Sodium nitrite Water   |                         | SA–NA                       | 0.3% 0.3%                      | Forestomach and spleen in both sex/species | Possible carcinogen; mutagen: focal hyperplasia of the squamous epithelium at the boundary of the forestomach and glandular stomach; extramedullary hematopoiesis of the spleen; sodium nitrite can interact with amines and amides to form nitroso compounds and nitrosamines that are known animal carcinogens; next highest dose in subchronic study selected as high dose in chronic study; moderate risk. |
| 7832-00-0              |                         | (+/−)                       |                                 |                                 |                                    |
| Tetrahydrofuran        | Inhalation              | SA--                        | 1800 ppm 1800 ppm              | Forestomach in both sex/species; liver in MM, FM | Unlikely carcinogen; nonmutagen: liver cytomegaly was the major lesion in all mice exposed to the highest subchronic dose (5000 ppm) which was accompanied by "narcosis"; the next lower dose, 1800 ppm, was selected as the chronic study high dose; if chronic liver cytomegaly and/or necrosis is minimal in mice, liver neoplasia is unlikely. |
| 109-99-9               |                         | (−/+ S9)                    |                                 |                                 |                                    |
| Vanadium pentoxide     | Inhalation              | SA–NA                       | 2 mg/m<sup>3</sup> 6 mg/m<sup>3</sup> | Lung, both sex/species; nose cavity and spleen in MR, FR | Possible carcinogen; nonmutagen: chronic hyperplasia and inflammation of the bronchiolar and alveolar epithelium accompanied by fibrosis; low to moderate risk related to spontaneous incidence of lung tumors in rats and mice. |
| 1314-62-1              |                         | (−/+ S9)                    |                                 |                                 |                                    |

<sup>a</sup> SA = structure activity, NA = not applicable
<sup>b</sup> Rats, Mice
<sup>c</sup> Major target organs
TENNANT AND SPALDING

Table 1. (Continued)

| Chemical name | Route of administration | Structural alert$^b$ | Maximum dose tested in chronic bioassay$^c$ | Subchronic histopathology$^d$ | Major target organs | Comments and basis for prediction |
|----------------|-------------------------|---------------------|---------------------------------------------|-------------------------------|---------------------|---------------------------------|
| Chloroprene    | Inhalation              | SA$^+$              | 80 ppm                                      | Nasal cavity and liver, MR, FR; forestomach, MM, FM | Possible carcinogen; nonmutagen: a chlorine-unsaturated carbon bond could yield an epoxide intermediate that could have an activity similar to its structural analog, 1,3-butadiene, a potent carcinogen in mice; the NOEL in the subchronic study was 32 ppm in both rats and mice. |
| 126-99-8       |                         | $-/-$               |                                             |                               |                     |                                 |
| Phenolphthalein$^f$ | Feed                  | SA$^-$              | 5.0%                                        | No histopathologic lesions in rats; bone marrow and spleen, MM, FM | Unlikely carcinogen; nonmutagen: no gross or histopathologic lesions observed in exposed rats; elevated incidence of microtubulated erythrocytes in mice suggests a genotoxic metabolite of the parent compound; cell depletion and necrosis occurred in mouse bone marrow; phenolphthalein is unlikely to be a carcinogen unless chronic high dose in mice causes neoplasia indirectly via physiological imbalance. |
| 77-09-6        |                         | $-/-$               |                                             |                               |                     |                                 |

$^a$All of the information used in these predictions, e.g., structures and subchronic toxicity, can be obtained through the NIEHS/NTP home pages: NIEHS: http://www.niehs.nih.gov/exchange/ and NTP: http://ntp-server.niehs.nih.gov/.  
$^b$Structural alert, SA (S): NA, criteria for determining structural alerts do not apply to inorganic compounds Sal. 
$^c$Salmonella mutagenicity assay performed with and without S9-induced liver microsome preparations.  
$^d$Maximum dose selected for chronic 2-year bioassay expressed as: %, ppm, mg/kg or ppm/meter(m)$^3$.  
$^e$Major target organs identified via histopathology in the 13-week subchronic study: male rat (MR); female rat (FR); male mouse (MM); female mouse (FM). NOEL = a "no effect level" was not reached in the subchronic study.  
$^f$Nine chemicals that have undergone peer review prior to submission of this manuscript.

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