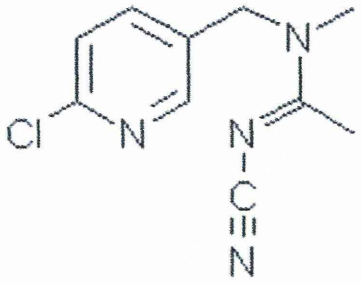
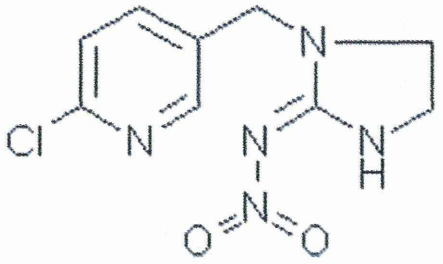


アセタミプリド



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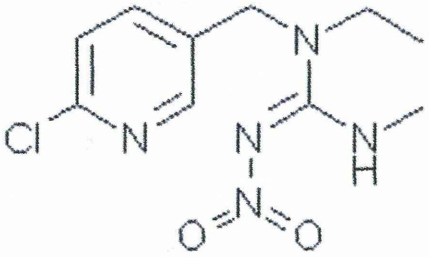
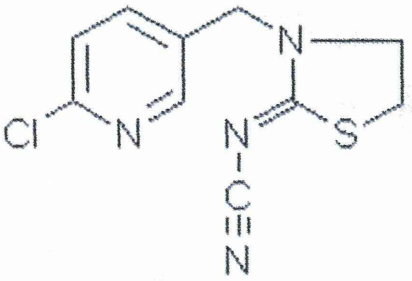
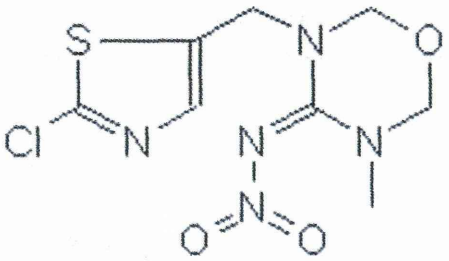


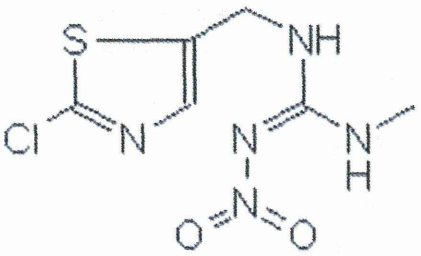
ニテンピラム



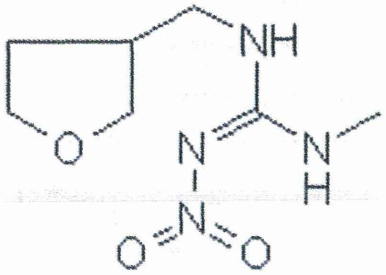
チアクロプリド



チアメトキサム



クロチアニジン

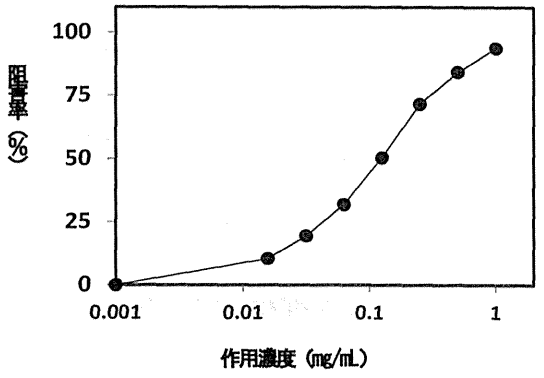


ジノテフラン

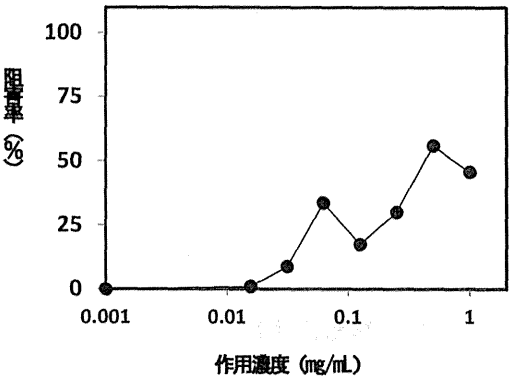
図１　ネオニコチノイド系殺虫剤の構造

「ネオニコチノイド系農薬・殺虫剤」便覧（http://no-neonico.jp/pdf/binran.pdf）より転載

アセタミプリド



イミダクロプリド



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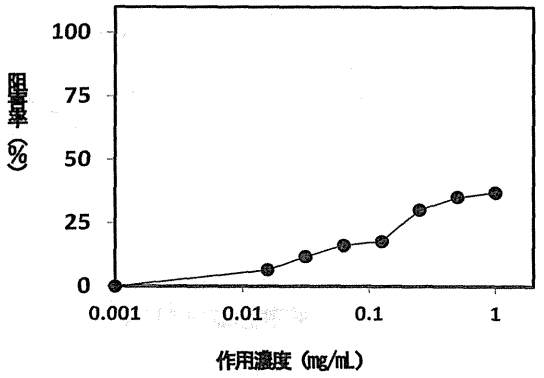

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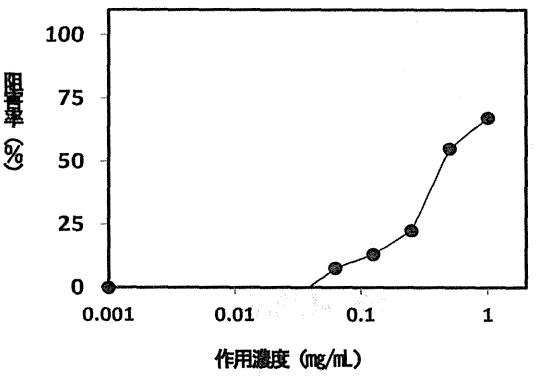
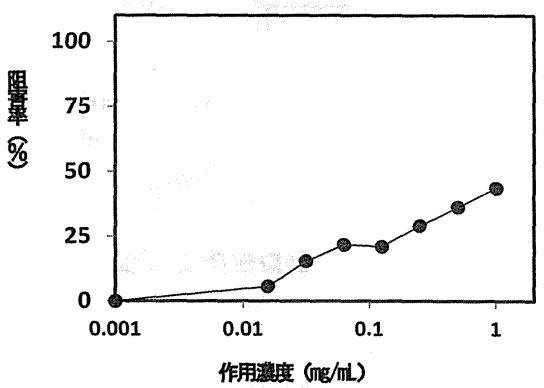
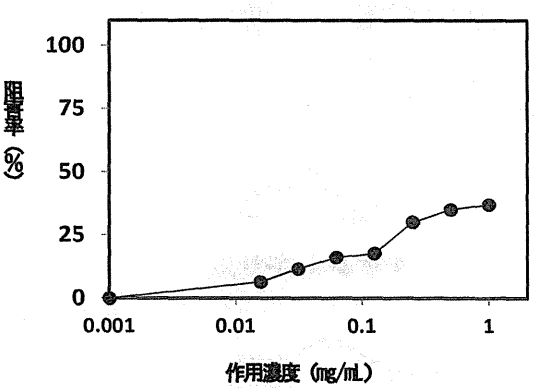


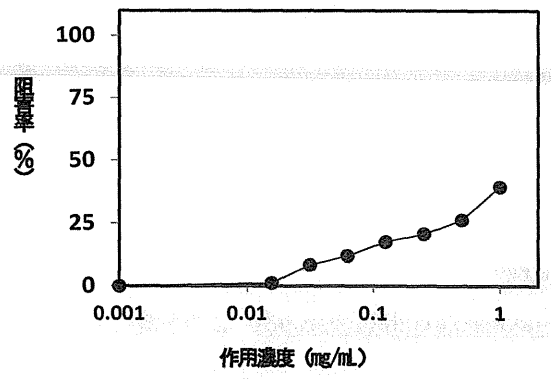
チアメトキサム



クロチアニジン



ジノテフラン



ダイアジノンオキソン

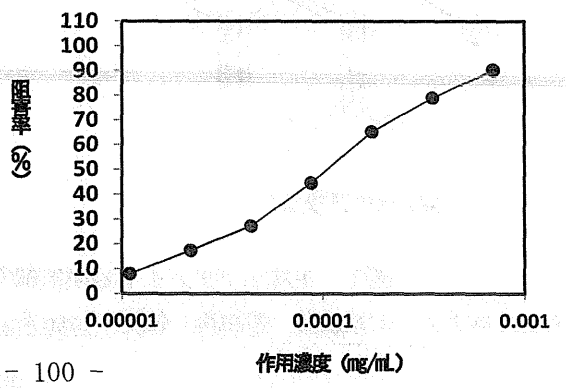


図2　ネオニコチノイド系殺虫剤とダイアジノンオキソンのAChE活性に対する阻害作用

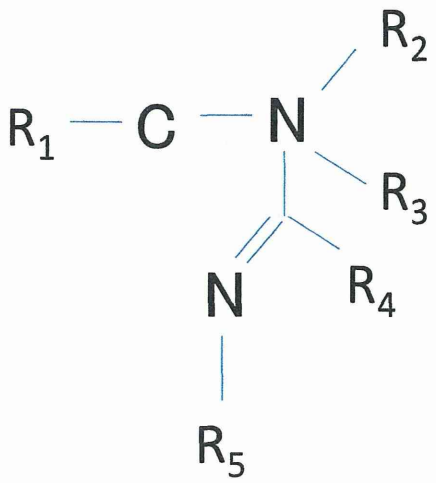


図3　ネオニコチノイド系殺虫剤の基本骨格

表1　ネオニコチノイド系殺虫剤のヒトAChE活性の阻害

物質名	最小毒性発現濃度(μg/mL)	評価濃度(mg/mL)	阻害割合相当のダイアジノンオキソン濃度(μg/mL)	相対毒性
アセタミプリド	15.6	0.125	0.11	8.8
イミダクロプリド	31.3	0.5	0.13	2.6
ニテンピラム	15.6	0.25	0.049	2
チアクロプリド	62.5	0.5	0.13	2.6
チアメトキサム	15.6	1	0.088	0.88
クロチアニジン	15.6	0.25	0.057	2.3
ジノテフラン	31.3	1	0.073	0.73

別添５

III.　研究成果の刊行に関する一覧表

別紙４

III. 研究成果の刊行に関する一覧表

雑誌

発表者氏名	論文タイトル名	発表誌名	巻号	ページ	出版年
T. Morita, A. Miyajima, A. Hatano, M. Honma	Effects of lowering the proposed top-concentration limit in an in vitro chromosomal aberration test on assay sensitivity and on the reduction of the number of false positives	*Mutation Research*	769	34-49	2014
D. Kirkland, E. Zeiger, F. Madia, N. Gooderham, P. Kasper, A. Lynch, T. Morita, G. Ouedraogo, J.M.P. Morte, S. Pfuhler, V. Rogiers, M. Schulz, V. Thybaud, J. Benthem, P. Vanparys, A. Worth, R. Corvi	Can in vitro mammalian cell genotoxicity test results be used to complement positive results in the Ames test and help predict carcinogenic or in vivo genotoxic activity? I. Reports of individual databases presented at an EURL ECVAM Workshop	*Mutation Research*	775-776	55-68	2014
Yamada, T., Tanaka, Y., Hasegawa, R., Sakuratani, Y., Yamazoe, Y., Ono, A., Hirose, A., Hayashi, M.	Development of a category approach to predict the testicular toxicity of chemical substances structurally related to ethylene glycol methyl ether	*Regul Toxicol Pharmacol*	70	711–719	2014
Kobayashi, K., Pillai, K., Michael, M., Cherian, K., Ono, A.	Transition of Japan's statistical tools by decision tree for quantitative data obtained from the general repeated dose administration toxicity studies in rodents	*International Journal of Basic and Applied Sciences*	3	507–520	2014

Matsumoto, M., Masumori, S., Hirata-K. M., Ono, A., Honma, M., Yokoyama, K., Hirose, A.	Evaluation of in vivo mutagenicity of hydroquinone in Muta™ mice.	*Mutat Res Genet Toxicol Environ Mutagen*	775-776	94–98	2014
Ema, M., Endoh, K., Fukushima, R., Fujii, S., Hara, H., Hirata-Koizumi, M., Hirose, A., Hojo, H., Horimoto, M., Hoshino, N., Hosokawa, Y., Imai, Y., Inada, H., Inawaka, K., Itoh, K., Katsumata, Y., Izumi, H., Kato, H., Maeda, M., Matsumoto, K., Matsuo, S., Matsuoka, T., Matsuura, I., Mineshima, H., Miwa, Y., Nakano, N., Naya, M., Noyori, H., Ohta, T., Oku, H., Ono, A., Shimizu, T., Shimomura, K., Takakura, I., Tanaka, R., Tateishi, T., Tominaga, Y., Uesugi, T., Urakawa, C., Yabe, K., Yamashita, A., Yamauchi, T., Yokoi, R.	Historical control data on developmental toxicity studies in rodents.	*Congenit Anom (Kyoto)*	54	150–161	2014
Takahashi, M., Ishida, S., Hirata-K. M., Ono, A., Hirose, A.	Repeated dose and reproductive/developmental toxicity of perfluoroundecanoic acid in rats.	*J Toxicol Sci*	39	97–108	2014

Petkov, PI, Patlewicz, G, Schultz, TW, Honma, M, Todorov, T, Kotov, S, Dimitrov, SD, Donner, M, Mekenyan, OG,	A feasibility study: Can information collected to classify for mutagenicity be informative in predicting carcinogenicity?	Regul. Tox. Pharm.,	72	17-25	2015

IV.　研究成果の刊行物・別刷

Mutation Research 769 (2014) 34–49

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Effects of lowering the proposed top-concentration limit in an *in vitro* chromosomal aberration test on assay sensitivity and on the reduction of the number of false positives

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ABSTRACT

For the *in vitro* chromosomal aberration (CA) test, the proposed top-concentration limit will be reduced to '10 mM or 2 mg/mL' (whichever is lower) in the draft revised OECD (r-OECD) test guideline (TG) 473, down from '10 mM or 5 mg/mL' in the current OECD TG, which was adopted in 1997 (1997-OECD). It was previously reduced to 1 mM or 0.5 mg/mL in the International Conference of Harmonization (ICH) S2 (R1) guideline for pharmaceuticals. Reduction of the top-concentration limit is expected to reduce the number of false or misleading positives. However, this reduction may affect the sensitivity or specificity to predict rodent carcinogenicity. Thus, the effect of a reduction in the top-concentration limit on sensitivity and specificity was investigated by use of a dataset on 435 chemicals obtained from the 'Carcinogenicity and Genotoxicity eXperience' (CGX) database (267 CA-positives and 168 CA-negatives; 317 carcinogens and 118 non-carcinogens) where three TGs (*i.e.*, 1997-OECD, r-OECD and ICH) were applied. The application of the r-OECD TG did not affect the sensitivity (63.1%) or specificity (59.3%) against carcinogenicity, compared with the 1997-OECD TG (sensitivity 63.1%, specificity 59.3%). However, the application of the ICH TG had certain effects, *i.e.*, a decrease in sensitivity (45.4%) and an increase in specificity (72.9%). A change in the number of CA-positives by the application of each TG was also investigated by use of 124 CA-positives from the Japanese Existing Chemical (JEC) database. The application of r-OECD TG showed a small reduction in CA-positives, but the ICH TG reduced this number by approximately half. More than half of the CA-positives had a molecular weight <200. These results suggest that the r-OECD TG will not affect the sensitivity or specificity for the detection of rodent carcinogens, indicating the usefulness of the guideline. However, nearly no improvement with respect to a reduction in the number of false positives should be expected.

1. Introduction

Unless limited by cytotoxicity or solubility, the top concentration suggested for use in the *in vitro* chromosomal aberration (CA) test has been 10 mM or 5 mg/mL (whichever is lower) in the Organization for Economic Co-operation and Development (OECD) test-guideline (TG) number 473 [1] for industrial chemicals and in the International Conference of Harmonization (ICH) S2A guideline [2] for pharmaceuticals, after recommendation from the first International Workshop on Genotoxicity Test Procedures (IWGTP) held in Melbourne in 1993 [3]. The 10-mM limit was defined as a limit that was low enough to avoid artificial increases in chromosomal damage due to excessive osmolality and was sufficiently high to ensure the detection of *in vivo* clastogens [4]. However, there has been much discussion on reducing of this top concentration-limit, in particular to diminish the number of false or misleading positive results obtained from mammalian cell genotoxicity tests in recent years [5–10]. Such results are the consequence of biologically non-relevant experimental conditions at very high concentrations used *in vitro*, *e.g.*, low pH, high osmolality, or precipitation of test material in the culture medium. Excessive cellular metabolism, activation or defense, and extremely high concentrations that would not be reached *in vivo* also induce false/misleading positives. Although several recommendations on the new top-concentration limits have been proposed, the recent ICH S2(R1) guideline for pharmaceuticals specified 1 mM or 0.5 mg/mL, whichever is lower, as the

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1383-5718/

concentration limit [11]. The rationale for a maximum concentration of 1 mM is as follows: (1) a test battery that includes the Ames test and an *in vivo* genotoxicity assay optimizes the detection of genotoxic carcinogens without relying on any individual assay alone. There is a very low likelihood that the compounds of concern (DNA-damaging carcinogens) – when they are not detected in the Ames test or an *in vivo* genotoxicity assay – can be detected in an *in vitro* mammalian assay above 1 mM; (2) a limit of 1 mM maintains the element of hazard identification, because it is higher than clinical exposures to known pharmaceuticals, including those concentrated in tissues, and is also above the levels generally achieved in preclinical studies *in vivo*. Even beyond the 1-mM limit, the *in vivo* tests ultimately determine the relevance for human safety. However, for pharmaceuticals with an unusually low molecular weight (*e.g.*, less than 200), higher test concentrations should be considered [11]. On the other hand, the draft revised OECD TG 473 proposes a limit of 10 mM or 2 mg/mL, whichever is lower [12]. The rationale for this top-concentration limit is based on the analysis of the data set generated by Parry et al. [6], suggesting that 10 mM is required to detect biologically relevant effects from lower molecular weight non-cytotoxic substances. A simulation study by Brookmire et al. [10] suggested that a test sensitivity at 10 mM is most similar to 2 mg/mL. These findings suggest that the combination of 10 mM or 2 mg/mL, whichever is lower, represents the best balance between the mM and mg/mL concentrations. For complex mixtures, the recommended top concentration remains 5 mg/mL. New top-concentration limits recommended by these TGs are expected to reduce the number of false or misleading positives. However, a reduction of the top-concentration limit may affect the sensitivity or specificity for rodent carcinogenicity, although this reduction should result in an improvement in the specificity of tests without a loss in sensitivity. Here, sensitivity is the ratio of positive *in vitro* CA test results to rodent carcinogens, while specificity is the ratio of negative *in vitro* CA test results to rodent non-carcinogens. In addition, a quantitative structure–activity relationship and software tools have been used recently for to predict genotoxicity [13]. Chromosome damage is also one of the predictive endpoints in in-silico models, *e.g.*, Deductive Estimation of Risk from Existing Knowledge (DEREK) [9,14] or TIssue MEtabolism Simulator (TIMES) [9,15]. Alerts for chromosome damage are based primarily on data from the *in vitro* CA test. Therefore, in-silico evaluation may be affected by changes (from positive to negative) in the CA data. Thus, the effects of reductions of the top-concentration limit on sensitivity and specificity were investigated by use of a set of chemical data, *i.e.*, the Carcinogenicity and Genotoxicity eXperience (CGX) database. To assess the effects in terms of reduction of potential false positives, another chemical data set, *i.e.*, the Japan Existing Chemical (JEC) database, which refers to the Chemical Substances Control Law (CSCL), was used to determine the usefulness of the reduction. These analyses, based on real data obtained from many different chemicals, will be useful for understanding the potential impact of changes in the top concentration used in the *in vitro* CA test.

2. Materials and methods

2.1. Databases used

2.1.1. CGX database

The CGX database provides genotoxicity information on 756 rodent carcinogens and 183 non-carcinogens [16]. The chemicals included in the database comprise all types of chemical, such as industrial chemicals, agrochemicals, pesticides, pharmaceuticals, natural products, and others. For some of these chemicals *in vitro* CA test data are available. The 756 carcinogens included 231 CA-positives, 107 CA-negatives and 14 CA-equivocal. In addition, the 183 non-carcinogens included 61 CA-positives, 61 CA-negatives and 14 CA-equivocal. Data for the *in vitro* CA test were obtained from compilations, such as that from Ishidate et al. [17], and from reports of NTP studies published by Galloway et al. [18], Loveday et al. [19,20], Anderson et al. [21] and other published literature in the CGX database [16]. Thus, various protocols were applied, with different cell types (CHO, CHL, human lymphocytes, etc.), sampling times, top-concentration limit, and cytotoxicity, or different applications of the test guideline or the Good Laboratory Practice (GLP) regulations. The lowest effective concentrations (LECs) were confirmed in all 292 CA-positives (231 carcinogens and 61 non-carcinogens) using the NTP database [22] or original studies [17–21,23–46]. The LEC was defined as the lowest concentration with a statistically significant induction of CA or with a 10% or more CA induction if no statistical analysis was performed, regardless of the test conditions, *e.g.*, different duration of treatment and the presence or absence of S9 mix. The rationale for selecting a 10% cut-off for a positive response is as follows: Ishidate classified test results as positive (≥10% cells with CAs), equivocal (≥5–10% cells with CAs) or negative (less than 5% cells with CAs) in the CA test using Chinese hamster lung (CHL) cells in a similar study protocol [24], and many test results by this author were cited in the CGX database [17]. The 10% cut-off rule is not fully applicable to other cell types with various background data on CA induction in different test protocols. However, it is reasonable to use this cut-off value in order to avoid any overestimation of the CA induction in this analysis. The molecular weight (MW) of each chemical substance was also recorded. When the LEC or MW of the chemical substance could not be identified due to the absence of any description in the paper, *e.g.*, in the case of chemical mixtures or polymers, the substance was excluded from the analysis. Thus, a total of 267 CA-positive chemicals (210 carcinogens and 57 non-carcinogens) were selected for analysis (Table 1). In addition, 168 CA-negatives (107 carcinogens and 61 non-carcinogens) from the CGX database [16] were included. The test concentrations were usually expressed as the weight per volume (*e.g.*, mg/mL). Therefore, LECs identified as mg/mL were converted to equivalent mol concentration (*e.g.*, mM) based on the MW of each chemical.

2.1.2. JEC database

The JEC database, which is based on CSCL regulations, provides toxicity information, *e.g.*, results of a 28-day repeat oral dose study, an Ames test or an *in vitro* CA test, on 277 Japanese existing chemicals (as of January 2012; test data generated from 1991 to 2007) [47]. All chemicals in the database are industrial chemicals with a high production volume in Japan. The *in vitro* CA test was performed with CHL cells according to the OECD TG 473 (first version 1983; revised version 1997 [1]) or the Japanese test guideline for new chemicals [24,48] under GLP conditions. LECs (mg/mL or mM) were defined as those in the CGX database. Of the 272 chemicals with *in vitro* CA data, 124 CA-positives and 148 CA-negatives were found according to their original call (evaluation). Importantly, the old Japanese test guideline employed a long exposure time (48-h of continuous treatment) and the assessment of numerical aberrations for polyploidy was the same as that recently found using TGs. The top-concentration limit was 5 mg/mL (or the equivalent of 10 mM) when no cytotoxicity was observed. The LECs in CA-positives or their MWs were confirmed by use of the original reports [47,49]. All chemicals were identified according to their LECs and MWs; thus, there were no exclusive chemicals identified from the analysis, and 124 CA-positives were used for the analysis (Table 2).

2.2. Application of the test guidelines

The following TGs issued by the OECD and ICH were applied in the analysis: (1) current OECD TG 473 adopted in 1997 (1997-OECD) [1], (2) draft revised OECD TG 473 (r-OECD) [12] for industrial chemicals and (3) ICH S2(R1) TG (ICH) [11] for pharmaceuticals. These TGs specify different top-concentration limits when not limited by solubility or cytotoxicity, namely, 10 mM or 5 mg/mL, whichever is lower, in the 1997-OECD; 10 mM or 2 mg/mL, whichever is lower, in the r-OECD; and 1 mM or 0.5 mg/mL, whichever is lower, in the ICH TG.

2.3. Sensitivity and specificity analyses

To analyze the sensitivity and specificity of the *in vitro* CA-test data against rodent carcinogenicity, a dataset on 435 chemicals (267 CA-positives and 168 CA-negatives; 317 carcinogens and 118 non-carcinogens) from the CGX database was used. Each LEC (in terms of mg/mL and mM) was applied to the three TGs, and the results were re-evaluated (positive or negative) based on the application of the concentration limit for each TG. The sensitivity and specificity against carcinogenicity were also calculated.

2.4. Analysis of the alterations in the number of CA-positives

Analysis of the altered numbers of CA-positives made use of 124 CA-positives from the JEC database. Each LEC (in terms of mg/mL and mM) was applied to the three TGs, and the results (positive or negative) were re-evaluated based on the application of the concentration limit of each TG.

2.5. Evaluation of the relevance of the in vitro CA results

The evaluation of the relevance of the *in vitro* CA results for the chemicals that showed 'different' results between the r-OECD (positive call) and ICH (negative call) TGs for chemicals from the JEC database, was based on a weight-of-evidence

Table 1
Re-evaluation of chromosomal aberration test results on the 267 CA-positive chemicals (210 carcinogens and 57 non-carcinogens).

CGX ID	C/NC	Chemical name	CAS no.	MW	CA (original call)	Equiv. to 10 mM (mg/mL)	LEC (mg/mL)	LEC (mM)	Ref.	1997-OECD[a]	r-OECD[b]	ICH[c]
										CA	CA	CA
1	C	*Acetaldehyde*	*75-07-0*	*44.1*	+	*0.44*	*0.0044*	*0.1*	*17*	+	+	+
2	C	*Acetaminophen*	*103-90-2*	*151.2*	+	*1.51*	*0.2*	*1.3*	*17*	+	+	- (+)
3	C	*N*-Acetoxy-2-acetylaminofluorene	6098-44-8	281.3	+	2.81	0.0003	0.001	17	+	+	+
4	C	2-Acetylaminofluorene	53-96-3	223.3	+	2.23	0.5	2.2	17	+	+	-
5	C	*Acrylamide*	*79-06-1*	*71.1*	+	*0.71*	*2*	*28.14*	*22*	-	-	-
6	C	*Acrylonitrile*	*107-13-1*	*53.1*	+	*0.53*	*0.0053*	*0.1*	*23*	+	+	+
7	C	Actinomycin D	50-76-0	1255.4	+	12.55	0.0018	0.0014	17	+	+	+
8	C	Aflatoxin B1	1162-65-8	312.3	+	3.12	0.0005	0.0016	17	+	+	+
9	C	Aldrin	309-00-2	364.9	+	3.65	0.019	0.052	17	+	+	+
10	C	*Allyl glycidyl ether*	*106-92-3*	*114.1*	+	*1.14*	*0.06*	*0.53*	*22*	+	+	+
11	C	*Allyl isothiocyanate*	*57-06-7*	*99.2*	+	*0.99*	*5.00E-07*	*0.000005*	*17*	+	+	+
12	C	*Allyl isovalerate*	*2835-39-4*	*142.2*	+	*1.42*	*0.3*	*2.11*	*22*	+	+	- (+)
13	C	*4-Aminobiphenyl*	*92-67-1*	*169.2*	+	*1.69*	*0.05*	*0.30*	*22*	+	+	+
14	C	3-Amino-1,4-dimethyl-5H-pyrido{4,3-b]indoleacetate (Trp-P-1 acetate)	68808-54-8	271.3	+	2.71	0.00125	0.0046	17	+	+	+
15	C	3-Amino-1-methyl-5H-pyrido{4,3-b]indoleacetate (Trp-P-2 acetate)	72254-58-1	257.3	+	2.57	0.05	0.019	17	+	+	+
16	C	*2-Amino-4-nitrophenol*	*99-57-0*	*154.1*	+	*1.54*	*0.015*	*0.1*	*17*	+	+	+
17	C	*2-Amino-5-nitrophenol*	*121-88-0*	*154.1*	+	*1.54*	*0.00375*	*0.024*	*17*	+	+	+
18	C	*4-Amino-2-nitrophenol*	*119-34-6*	*154.1*	+	*1.54*	*0.16*	*1.04*	*22*	+	+	- (+)
19	C	*2-Amino-5-nitrothiazole*	*121-66-4*	*145.1*	+	*1.45*	*0.1*	*0.69*	*22*	+	+	+
20	C	Atrazine	1912-24-9	215.7	+	2.16	0.0184	0.085	24	+	+	+
21	C	Auramine O	2465-27-2	303.8	+	3.04	0.0064	0.02	25	+	+	+
22	C	5-Azacytidine	320-67-2	244.2	+	2.44	0.002	0.008	17	+	+	+
23	C	Azathioprine	446-86-6	277.3	+	2.77	0.023	0.083	17	+	+	+
24	C	*Benzaldehyde*	*100-52-7*	*106.1*	+	*1.06*	*5.00E-06*	*0.00005*	*17*	+	+	+
25	C	*Benzene*	*71-43-2*	*78.1*	+	*0.78*	*0.009*	*0.11*	*17*	+	+	+
26	C	*Benzidine*	*92-87-5*	*184.2*	+	*1.84*	*0.0025*	*0.014*	*17*	+	+	+
27	C	Benzidine 2HCl	531-85-1	257.2	+	2.57	0.003	0.12	19	+	+	+
28	C	Benzo[*a*]pyrene	50-32-8	252.3	+	2.52	0.005	0.02	17	+	+	+
29	C	*Benzyl chloride*	*100-44-7*	*126.6*	+	*1.27*	*0.015*	*0.12*	*17*	+	+	+
30	C	2-Biphenylamine HCl	2185-92-4	205.7	+	2.06	0.2	0.97	22	+	+	+
31	C	2,2-Bis(bromomethyl)-1,3-propanediol, technical grade	3296-90-0	261.9	+	2.62	0.8	3.05	18	+	+	-
32	C	*Bis(2-chloro-1-methylethyl)ether, technical grade*	*108-60-1*	*171.1*	+	*1.71*	*0.124*	*0.72*	*22*	+	+	+
33	C	Bis(2,3-dibromopropyl)phosphate, magnesium salt	36711-31-6	201.4	+	2.01	2	9	17	+	+	-
34	C	*Bromate, potassium*	*7758-01-2*	*167.0*	+	*1.67*	*0.0625*	*0.37*	*17*	+	+	+
35	C	*Bromodichloromethane*	*75-27-4*	*163.8*	+	*1.64*	*0.24*	*1.5*	*17*	+	+	- (+)
36	C	*Butylated hydroxyanisole*	*25013-16-5*	*180.3*	+	*1.80*	*0.125*	*0.69*	*26*	+	+	+
37	C	*N-n-Butyl-N-nitrosourea*	*869-01-2*	*145.2*	+	*1.45*	*0.1*	*0.7*	*17*	+	+	+
38	C	*Cadomium cholride*	*10108-64-2*	*183.3*	+	*1.83*	*0.0055*	*0.03*	*17*	+	+	+
39	C	Cadomium sulphate	10124-36-4	208.5	+	2.09	0.02	0.1	17	+	+	+
40	C	*Calcium chromate*	*13765-19-0*	*156.0*	+	*1.56*	*0.00015*	*0.001*	*17*	+	+	+
41	C	Carbaryl	63-25-2	201.2	+	2.01	0.015	0.075	17	+	+	+
42	C	*Carboxymethylnitrosourea*	*60391-92-6*	*147.1*	+	*1.47*	*0.0625*	*0.42*	*17*	+	+	+
43	C	*Caffeic acid*	*331-39-5*	*180.2*	+	*1.80*	*0.26*	*1.4*	*17*	+	+	- (+)
44	C	Captafol	2425-06-1	349.1	+	3.49	0.0035	0.01	17	+	+	+
45	C	Captan	133-06-2	300.6	+	3.00	0.007	0.023	17	+	+	+
46	C	*Chloral hydrate*	*302-17-0*	*165.4*	+	*1.65*	*0.6*	*3.63*	*27*	+	+	- (+)
47	C	Chloramben	133-90-4	206.0	+	2.06	1.51	7.33	22	+	+	-
48	C	Chlorambucil	305-03-3	304.2	+	3.04	0.00025	0.0008	17	+	+	+
49	C	Chlorendic acid	115-28-6	388.8	+	3.89	1.95	5.015	28	+	+	-

50	C	*Chlorobenzene*	*108-90-7*	*112.6*	+	*1.13*	*0.15*	*1.33*	*19*	+	+	- (+)
51	C	Chlorodibromomethane	124-48-1	208.3	+	2.08	0.72	3.457	28	+	+	-
52	C	*3-Chloro-2-methylpropene, technical grade*	*563-47-3*	*90.6*	+	*0.91*	*0.12*	*1.33*	*22*	+	+	- (+)
53	C	*3-(Chloromethyl)pyridine HCl*	*6959-48-4*	*164.0*	+	*1.64*	*0.05*	*0.30*	*22*	+	+	+
54	C	*1-Chloro-4-nitrobenzene*	*100-00-5*	*157.6*	+	*1.58*	*0.6*	*3.81*	*22*	+	+	- (+)
55	C	*3-(p-Chlorophenyl)-1,1-dimethylurea*	*150-68-5*	*198.7*	+	*1.99*	*1.3*	*6.54*	*22*	+	+	- (+)
56	C	*4-Chloro-m-phenylenediamine*	*5131-60-2*	*142.6*	+	*1.43*	*0.525*	*3.68*	*20*	+	+	- (+)
57	C	*4-Chloro-o-phenylenediamine*	*95-83-0*	*142.6*	+	*1.43*	*0.0101*	*0.07*	*20*	+	+	+
58	C	Chlorothalonil	1897-45-6	265.9	+	2.66	0.0005	0.002	22	+	+	+
59	C	Chrysazin	81-55-0	330.2	+	3.30	0.005	0.02	22	+	+	+
60	C	C.I. Acid orange 3	6373-74-6	452.4	+	4.52	0.0891	0.20	22	+	+	+
61	C	C.I. Disperse blue 1	2475-45-8	268.3	+	2.68	0.0075	0.03	22	+	+	+
62	C	C.I. Disperse orange 2 (1-amino-2-methyl-anthrquinone)	82-28-0	237.3	+	2.37	0.3	1.26	22	+	+	-
63	C	Ciprofibrate	52214-84-3	289.2	+	2.89	0.0289	0.1	29	+	+	+
64	C	Clofibrate	637-07-0	242.7	+	2.43	0.25	1	17	+	+	+
65	C	*Coumarin*	*91-64-5*	*146.2*	+	*1.46*	*1.6*	*10.95*	*18*	-	-	-
66	C	*m-Cresidine*	*102-50-1*	*137.2*	+	*1.37*	*0.5*	*3.64*	*22*	+	+	- (+)
67	C	*Cupferron*	*135-20-6*	*155.2*	+	*1.55*	*1.163*	*7.50*	*22*	+	+	- (+)
68	C	Cytembena	21739-91-3	307.1	+	3.07	0.0249	0.08	22	+	+	+
69	C	Danthron	117-10-2	240.2	+	2.40	0.017	0.07	22	+	+	+
70	C	*p,p'*-DDE	72-55-9	318.0	+	3.18	0.0088	0.028	17	+	+	+
71	C	DDT	50-29-3	354.5	+	3.55	0.0081	0.023	17	+	+	+
72	C	2,4-Diaminoanisole sulphate	39156-41-7	236.2	+	2.36	0.06	0.025	17	+	+	+
73	C	*2,4-Diaminotoluene*	*95-80-7*	*122.2*	+	*1.22*	*0.0985*	*0.81*	*20*	+	+	+
74	C	1,2-Dibromo-3-chloropropane	96-12-8	236.3	+	2.36	0.047	0.2	17	+	+	+
75	C	*1,2-Dibromoethane*	*106-93-4*	*187.9*	+	*1.88*	*0.38*	*2*	*17*	+	+	- (+)
76	C	Dibromomannitol	488-41-5	308.0	+	3.08	0.15	0.49	22	+	+	+
77	C	1,3-Dibutyl-1-nitrosourea	56654-52-5	201.3	+	2.01	0.0625	0.31	17	+	+	+
78	C	*Dichloroacetic acid*	*79-43-6*	*128.9*	+	*1.29*	*1.25*	*9.69*	*27*	+	+	- (+)
79	C	*1,2-Dichloroethane*	*107-06-2*	*99.0*	+	*0.99*	*0.5*	*5.05*	*22*	+	+	- (+)
80	C	*Dichloromethane*	*75-09-2*	*84.9*	+	*0.85*	*0.0005*	*0.06*	*17*	+	+	+
81	C	*2,6-Dichloro-p-phenylenediamine*	*609-20-1*	*177.0*	+	*1.77*	*0.25*	*1.41*	*22*	+	+	- (+)
82	C	*1,2-Dichloropropane*	*78-87-5*	*113.0*	+	*1.13*	*0.66*	*5.84*	*22*	+	+	- (+)
83	C	Dichlorvos	62-73-7	221.0	+	2.21	0.01	0.045	17	+	+	+
84	C	Dieldrin	60-57-1	380.9	+	3.81	0.001	0.003	17	+	+	+
85	C	Diethylstilbestrol	56-53-1	268.4	+	2.68	0.0001	0.00037	17	+	+	+
86	C	Diglycidyl resorcinol ether, technical grade	101-90-6	222.2	+	2.22	0.0005	0.002	22	+	+	+
87	C	*Dimethoxane*	*828-00-2*	*174.2*	+	*1.74*	*0.0126*	*0.07*	*22*	+	+	+
88	C	3,3'-Dimethoxybenzidine-4,4'-diisocyante	91-93-0	296.3	+	2.96	0.093	0.31	22	+	+	+
89	C	*N,N*-Dimethyl-4-aminoazobenzene	60-11-7	225.3	+	2.25	0.025	0.11	17	+	+	+
90	C	*N,N-Dimethylaniline*	*121-69-7*	*121.2*	+	*1.21*	*0.083*	*0.69*	*19*	+	+	+
91	C	7,12-Dimethylbenz[*a*]anthracene	57-97-6	256.4	+	2.56	0.001	0.0039	17	+	+	+
92	C	3,3'-Dimethylbenzidine	119-93-7	212.3	+	2.12	0.46	2.17	22	+	+	-
93	C	3,3'-Dimethylbenzidine 2HCl	612-82-8	285.2	+	2.85	0.005	0.02	22	+	+	+
94	C	*Dimethylcarbamoyl chloride*	*79-44-7*	*107.5*	+	*1.08*	*0.02*	*0.185*	*17*	+	+	+
95	C	*Dimethyl hydrogen phosphite*	*868-85-9*	*110.0*	+	*1.10*	*1.6*	*14.54*	*22*	-	-	-
96	C	*Epichlorhydrin*	*106-89-8*	*92.5*	+	*0.93*	*0.005*	*0.054*	*17*	+	+	+
97	C	*1,2-Epoxybutane*	*106-88-7*	*92.5*	+	*0.93*	*0.05*	*0.54*	*22*	+	+	+
98	C	*Ethionamide*	*536-33-4*	*166.2*	+	*1.66*	*0.4*	*2.4*	*17*	+	+	- (+)
99	C	*Ethyl acrylate*	*140-88-5*	*100.1*	+	*1.00*	*0.011*	*0.11*	*17*	+	+	+
100	C	*Ethylene oxide*	*75-21-8*	*44.1*	+	*0.44*	*0.22*	*5*	*17*	+	+	- (+)

Table 1 (*Continued*)

CGX ID	C/NC	Chemical name	CAS no.	MW	CA (original call)	Equiv. to 10 mM (mg/mL)	LEC (mg/mL)	LEC (mM)	Ref.	1997-OECD[a]	r-OECD[b]	ICH[c]
										CA	CA	CA
101	*C*	*Ethyl methanesulphonate*	*62-50-0*	*124.2*	+	*1.24*	*3.00E-06*	*0.000024*	*17*	+	+	+
102	*C*	*N-Ethyl-N'-nitro-N-nitrosoguanidine*	*63885-23-4*	*161.1*	+	*1.61*	*0.0025*	*0.016*	*17*	+	+	+
103	*C*	*1-Ethyl-1-nitrosourea*	*759-73-9*	*117.1*	+	*1.17*	*0.0117*	*0.1*	*17*	+	+	+
104	*C*	*5-Fluorouracil*	*51-21-8*	*130.1*	+	*1.30*	*0.001*	*0.008*	*17*	+	+	+
105	*C*	*Formaldehyde*	*50-00-0*	*30.0*	+	*0.30*	*0.006*	*0.2*	*17*	+	+	+
106	C	Fumonisin B1	116355-83-0	721.8	+	7.22	0.001	0.0014	30	+	+	+
107	*C*	*Furan*	*110-00-9*	*68.1*	+	*0.68*	*0.16*	*2.35*	*22*	+	+	- (+)
108	*C*	*Furfural*	*98-01-1*	*96.1*	+	*0.96*	*0.2*	*2.08*	*22*	+	+	- (+)
109	C	Furosemide	54-31-9	330.7	+	3.31	2	6	17	+	+	-
110	C	Furylfuramide (AF-2)	3688-53-7	248.2	+	2.48	0.005	0.02	17	+	+	+
111	*C*	*Glycidol*	*556-52-5*	*74.1*	+	*0.74*	*0.03*	*0.4*	*17*	+	+	+
112	C	Griseofulvin	126-07-8	352.8	+	3.53	0.04	0.11	17	+	+	+
113	C	Haloperidol	52-86-8	375.9	+	3.76	0.01	0.026	31	+	+	+
114	C	HC Blue 1 (impure and purified)	2784-94-3	255.3	+	2.55	0.96	3.76	20	+	+	-
115	C	Heptachlor	76-44-8	373.3	+	3.73	0.025	0.07	22	+	+	+
116	*C*	*Hexanamide*	*628-02-4*	*115.2*	+	*1.15*	*4*	*34.73*	*22*	-	-	-
117	*C*	*Hydrazine sulphate*	*10034-93-2*	*130.1*	+	*1.30*	*0.158*	*1.2*	*17*	+	+	- (+)
118	*C*	*Hydrazobenzene*	*122-66-7*	*184.2*	+	*1.84*	*0.0014*	*0.01*	*22*	+	+	+
119	*C*	*Hydrogen peroxide*	*7722-84-1*	*34.0*	+	*0.34*	*0.00034*	*0.01*	*17*	+	+	+
120	C	N-Hydroxy-2-acetylaminofluorene	53-95-2	239.3	+	2.39	0.001	0.0042	17	+	+	+
121	*C*	*Isobutyl nitrite*	*542-56-3*	*103.1*	+	*1.03*	*0.051*	*0.49*	*22*	+	+	+
122	*C*	*Isoniazid*	*54-85-3*	*137.1*	+	*1.37*	*0.44*	*3.2*	*17*	+	+	- (+)
123	*C*	*Isophorone*	*78-59-1*	*138.2*	+	*1.38*	*1.25*	*9.044*	*28*	+	+	- (+)
124	C	Lasiocarpine	303-34-4	411.5	+	4.12	0.206	0.5	17	+	+	+
125	C	Lead acetate	301-04-2	325.3	+	3.25	0.0033	0.01	17	+	+	+
126	C	Manganese ethylenebisthiocarbamate	12427-38-2	265.3	+	2.65	0.015	0.057	17	+	+	+
127	C	Melphalan	148-82-3	305.2	+	3.05	0.0001	0.0033	17	+	+	+
128	*C*	*2-Mercaptobenzothiazole*	*149-30-4*	*167.2*	+	*1.67*	*0.374*	*2.23*	*22*	+	+	- (+)
129	C	Methapyrilene hydrochloride	135-23-9	297.8	+	2.98	0.747	2.51	22	+	+	-
130	*C*	*Methimazole*	*60-56-0*	*114.2*	+	*1.14*	*0.37*	*3.2*	*17*	+	+	- (+)
131	*C*	*4-Methoxyphenol*	*150-76-5*	*124.1*	+	*1.24*	*0.031*	*0.25*	*32*	+	+	+
132	C	8-Methoxypsoralen	298-81-7	216.2	+	2.16	0.1	0.46	22	+	+	+
133	*C*	*Methylazoxymethanol acetate*	*592-62-1*	*132.1*	+	*1.32*	*0.00013*	*0.001*	*17*	+	+	+
134	*C*	*alpha-Methylbenzyl alcohol*	*98-85-1*	*122.2*	+	*1.22*	*1*	*8.19*	*22*	+	+	- (+)
135	C	3-Methylcholanthrene	56-49-5	268.3	+	2.68	0.002	0.0075	17	+	+	+
136	C	3'-Methyl-4-dimethylaminoazobenzene	55-80-1	239.3	+	2.39	0.05	0.21	17	+	+	+
137	C	4,4'-Methylenedianiline 2HCl	13552-44-8	271.2	+	2.71	0.8	2.95	22	+	+	-
138	*C*	*Methyl methanesulphonate*	*66-27-3*	*110.1*	+	*1.10*	*3.00E-06*	*0.000027*	*17*	+	+	+
139	C	2-Methyl-1-nitroanthraquinone	129-15-7	267.2	+	2.67	0.005	0.02	22	+	+	+
140	*C*	*N-Methyl-N'-nitro-N-nitrosoguanidine*	*70-25-7*	*147.1*	+	*1.47*	*3.00E-06*	*0.00002*	*17*	+	+	+
141	*C*	*Methylnitrosocyanamide*	*33868-17-6*	*85.1*	+	*0.85*	*0.00085*	*0.01*	*17*	+	+	+
142	*C*	*N-Methylolacrylamide*	*924-42-5*	*101.1*	+	*1.01*	*0.25*	*2.47*	*22*	+	+	- (+)
143	C	Methylphenidate HCl	298-59-9	267.0	+	2.67	1	3.71	18	+	+	-
144	*C*	*Metronidazole*	*443-48-1*	*171.2*	+	*1.71*	*0.0001*	*0.0006*	*33*	+	+	+
145	C	Mitomycin C	50-07-7	334.3	+	3.34	0.00017	0.00005	17	+	+	+
146	C	Monocrotaline	315-22-0	325.4	+	3.25	0.065	0.2	17	+	+	+
147	C	Nafenopin	3771-19-5	310.4	+	3.10	0.0093	0.03	29	+	+	+
148	*C*	*Naphthalene*	*91-20-3*	*128.2*	+	1.28	*0.03*	*0.23*	*22*	+	+	+
149	*C*	*1,5-Naphthalenediamine*	*2243-62-1*	*158.2*	+	1.58	*0.001*	*0.01*	*22*	+	+	+
150	*C*	*2-Naphthylamine*	*91-59-8*	*143.2*	+	1.43	*0.00333*	*0.023*	*17*	+	+	+
151	*C*	*Nitrite sodium*	*7632-00-0*	*69.0*	+	0.69	*4*	*58.0*	*17*	-	-	-
152	*C*	*o-Nitroanisole*	*91-23-6*	*153.1*	+	1.53	*1.06*	*6.92*	*18*	+	+	- (+)

153	C	Nitrobenzene	98-95-3	123.1	+	1.23	6.15	50	34	-	-	-
154	C	6-Nitrobenzimidazole	94-52-0	163.1	+	1.63	0.5	3.06	22	+	+	- (+)
155	C	p-Nitrobenzoic acid	62-23-7	167.1	+	1.67	0.875	5.24	22	+	+	- (+)
156	C	5-Nitro-2-furaldehyde semicarbazone	59-87-0	198.1	+	1.98	0.023	0.12	22	+	+	+
157	C	1-[(5-nitrofurfurylidene)amino]hydantoin	67-20-9	238.2	+	2.38	0.747	3.14	22	+	+	-
158	C	Nitrogen mustard	51-75-2	156.1	+	1.56	0.00002	0.0001	17	+	+	+
159	C	2-Nitro-p-phenylenediamine	5307-14-2	153.1	+	1.53	0.3	1.96	22	+	+	- (+)
160	C	1-Nitropyrene	5522-43-0	247.2	+	2.47	0.1	0.404	35	+	+	+
161	C	4-Nitroquinoline-N-oxide	56-57-5	190.2	+	1.90	0.00002	0.00011	17	+	+	+
162	C	p-Nitrosodiphenylamine	156-10-5	198.2	+	1.98	0.00025	0.0013	22	+	+	+
163	C	N-Nitrosodiethylamine (diethylnitrosamine)	55-18-5	102.1	+	1.02	3	29	17	-	-	-
164	C	N-Nitrosodimethylamine (dimethylnitrosamine)	62-75-9	74.1	+	0.74	0.5	6.7	17	+	+	- (+)
165	C	N-Nitroso-N-methylurea	684-93-5	103.1	+	1.03	0.01	0.1	17	+	+	+
166	C	5-Nitro-o-toluidine	99-55-8	152.2	+	1.52	0.5	3.29	22	+	+	- (+)
167	C	4,4'-Oxydianiline	101-80-4	200.2	+	2.00	0.1	0.50	22	+	+	+
168	C	N-Oxydiethylene thiocarbamyl-N-oxydiethylene sulphenamide	13752-51-7	248.4	+	2.48	0.005	0.02	17	+	+	+
169	C	Pentachloroethane	76-01-7	202.3	+	2.02	0.008	0.395	28	+	+	+
170	C	Pentachloronitrobenzene	82-68-8	295.3	+	2.95	0.0024	0.01	22	+	+	+
171	C	Petasitenine	60102-37-6	381.4	+	3.81	1.91	5	17	+	+	-
172	C	Phenacetin	62-44-2	179.2	+	1.79	0.4	2.2	17	+	+	- (+)
173	C	Phenazopyridine HCl	136-40-3	249.7	+	2.50	0.105	0.42	22	+	+	+
174	C	Phenobarbital	50-06-6	232.2	+	2.32	0.1	0.43	17	+	+	+
175	C	Phenolphthalein	28-37-6	318.3	+	3.18	0.05	0.16	22	+	+	+
176	C	Phenoxybenzamine HCl	63-92-3	340.3	+	3.40	0.03	0.09	22	+	+	+
177	C	Phenylbutazone	50-33-9	308.4	+	3.08	1.6	5.19	18	+	+	-
178	C	o-Phenylphenol	90-43-7	170.2	+	1.70	0.1	0.59	25	+	+	+
179	C	Propane sultone	1120-71-4	122.1	+	1.22	0.012	0.1	17	+	+	+
180	C	beta-Propiolactone	57-57-8	72.1	+	0.72	0.03	0.42	17	+	+	+
181	C	1,2-Propylene oxide	75-56-9	58.1	+	0.58	0.5	8.61	22	+	+	- (+)
182	C	N-Propyl-N'-nitro-N-nitrosoguanidine	13010-07-6	175.2	+	1.75	0.01	0.057	17	+	+	+
183	C	Pyrimethamine	58-14-0	248.7	+	2.49	0.05	0.201	36	+	+	+
184	C	Quercetin	117-39-5	302.2	+	3.02	0.006	0.02	17	+	+	+
185	C	p-Quinone dioxime	105-11-3	138.1	+	1.38	0.01	0.07	22	+	+	+
186	C	Retinol acetate	127-47-9	328.5	+	3.29	0.0656	0.2	23	+	+	+
187	C	Saccharin, sodium	128-44-9	205.2	+	2.05	8	39	17	-	-	-
188	C	Safrole	94-59-7	162.2	+	1.62	0.0833	0.5	17	+	+	+
189	C	Selenium sulphide	7446-34-6	111.0	+	1.11	0.0005	0.0045	20	+	+	+
190	C	Sodium dichromate	10588-01-9	262.0	+	2.62	0.0001	0.0019	17	+	+	+
191	C	Styrene	100-42-5	104.2	+	1.04	0.25	2.4	17	+	+	- (+)
192	C	Styrene oxide	96-09-3	120.2	+	1.20	0.00375	0.031	17	+	+	+
193	C	1,1,1,2-Tetrachloroethane	630-20-6	167.8	+	1.68	0.1	0.596	28	+	+	+
194	C	12-O-tetradecanoylphorbol 13-acetate	16561-29-8	616.8	+	6.17	6.20E-06	0.00001	17	+	+	+
195	C	Tertanitromethane	509-14-8	196.0	+	1.96	0.02	0.10	22	+	+	+
196	C	4,4'-Thiodianiline	139-65-1	216.3	+	2.16	0.1	0.46	22	+	+	+
197	C	Thio-tepa	52-24-4	189.2	+	1.89	0.00094	0.0049	17	+	+	+
198	C	o-Toluidine	95-53-4	107.2	+	1.07	0.012	0.13	17	+	+	+
199	C	Trenimon	68-76-8	231.3	+	2.31	1.00E-08	4.3E-08	17	+	+	+
200	C	Triamterene	396-01-0	253.3	+	2.53	0.00375	0.015	17	+	+	+
201	C	Tribromomethane	75-25-2	252.7	+	2.53	0.116	0.46	17	+	+	+
202	C	1,1,2-Trichloroethane	79-00-5	133.4	+	1.33	0.377	2.83	22	+	+	- (+)
203	C	N-(Trichloromethylthio)phthalimide	133-07-3	296.6	+	3.00	0.005	0.017	37	+	+	+
204	C	1,2,3-Trichloropropane	96-18-4	147.4	+	1.47	0.0595	0.40	22	+	+	+

Table 1 (*Continued*)

CGX ID	C/NC	Chemical name	CAS no.	MW	CA (original call)	Equiv. to 10 mM (mg/mL)	LEC (mg/mL)	LEC (mM)	Ref.	1997-OECD[a]	r-OECD[b]	ICH[c]
										CA	CA	CA
205	*C*	*2,4,5-Trimethylaniline*	*137-17-7*	*135.2*	+	*1.35*	*0.415*	*3.07*	*20*	+	+	- (+)
206	*C*	*Trimethylphosphate*	*512-56-1*	*140.1*	+	*1.40*	*3*	*21.42*	*22*	-	-	-
207	C	Tris(2,3-dibromopropyl)phosphate	126-72-7	697.9	+	6.98	0.125	0.18	17	+	+	+
208	*C*	*Urethane*	*51-79-6*	*89.1*	+	*0.89*	*8*	*90*	*17*	-	-	-
209	C	Zearalenone	17924-92-4	318.4	+	3.18	0.015	0.05	22	+	+	+
210	C	Zinc dimethyldithioearbamate (Ziram)	137-30-4	305.8	+	3.06	0.000025	0.00008	22	+	+	+
211	NC	Acetohexamide	968-81-0	324.4	+	3.24	2	6	17	+	+	-
212	*NC*	*o-Anthranilic acid*	*118-92-3*	*137.1*	+	*1.37*	*4*	*29.2*	*22*	-	-	-
213	*NC*	*Benzoate, sodium*	*532-32-1*	*144.1*	+	*1.44*	*0.29*	*2*	*17*	+	+	- (+)
214	NC	Benzoin	119-53-9	212.2	+	2.12	0.02	0.1	17	+	+	+
215	*NC*	*1H-Benzotriazole*	*95-14-7*	*119.1*	+	*1.19*	*1.257*	*10.55*	*22*	-	-	-
216	*NC*	*Benzyl alcohol*	*100-51-6*	*108.1*	+	*1.08*	*4*	*36.99*	*22*	-	-	-
217	*NC*	*Caffeine*	*58-08-2*	*194.2*	+	*1.94*	*0.08*	*0.4*	*17*	+	+	+
218	NC	Carbromal	77-65-6	237.1	+	2.37	1	4.22	22	+	+	-
219	NC	4-(Chloroacetyl)-acetanilide	140-49-8	211.6	+	2.12	0.0025	0.01	22	+	+	+
220	*NC*	*p-Chloroaniline*	*106-47-8*	*127.6*	+	*1.28*	*0.5*	*3.92*	*22*	+	+	- (+)
221	*NC*	*o-Chlorobenzalmalonitrile*	*2698-41-1*	*188.6*	+	*1.89*	*0.006*	*0.03*	*22*	+	+	+
222	*NC*	*2-(Chloromethyl)pyridine HCl*	*6959-47-3*	*164.0*	+	*1.64*	*0.0302*	*0.18*	*22*	+	+	+
223	NC	Chlorpheniramine maleate	113-92-8	390.9	+	3.91	0.5	1.28	22	+	+	-
224	NC	Chlorpropamide	94-20-2	276.7	+	2.77	1	3.6	17	+	+	-
225	NC	C.I. acid orange 10	1936-15-8	452.4	+	4.52	1.25	2.76	22	+	+	-
226	NC	Diallyl phthalate	131-17-9	246.3	+	2.46	0.2	0.81	22	+	+	+
227	NC	2,5-Diaminotoluen sulphate	6369-59-1	220.3	+	2.20	0.04	0.18	22	+	+	+
228	*NC*	*2,6-Diaminotoluene 2HCl*	*15481-70-6*	*195.1*	+	*1.95*	*1*	*5.13*	*22*	+	+	- (+)
229	NC	Diazinon	333-41-5	304.4	+	3.04	0.1	0.32	17	+	+	+
230	*NC*	*2,4-Dichlorophenol*	*120-83-2*	*163.0*	+	*1.63*	*0.0978*	*0.6*	*38*	+	+	+
231	NC	Dimethoate	60-51-5	229.2	+	2.29	0.5	2.2	17	+	+	-
232	*NC*	*Dimethoxane, commercial grade*	*828-00-2*	*174.2*	+	*1.74*	*0.0126*	*0.07*	*22*	+	+	+
233	*NC*	*2,4-Dimethoxyaniline HCl*	*54150-69-5*	*189.6*	+	*1.90*	*0.5*	*2.64*	*22*	+	+	- (+)
234	NC	Diphenhydramine HCl	147-24-0	291.8	+	2.92	0.1	0.34	22	+	+	+
235	NC	Diphenyl-*p*-phenylenediamine	74-31-7	260.3	+	2.60	0.001	0.0038	39	+	+	+
236	NC	Ethyl tellurac	20941-65-5	720.7	+	7.21	0.000032	0.00004	22	+	+	+
237	*NC*	*Eugenol*	*97-53-0*	*164.2*	+	*1.64*	*0.125*	*0.76*	*18*	+	+	+
238	NC	FD & C red no. 3 (MW as anhydrous)	16423-68-0	879.9	+	8.80	0.6	0.68	17	+	+	-
239	NC	FD & C yellow no. 5 [AKA tartrazine]	1934-21-0	534.4	+	5.34	2	3.7	17	+	+	-
240	NC	Fenthion	55-38-9	278.3	+	2.78	0.0015	0.005	40	+	+	+
241	NC	Fenvalerate	51630-58-1	419.9	+	4.20	0.01	0.024	41	+	+	+
242	*NC*	*Fluoride sodium*	*7681-49-4*	*42.0*	+	*0.42*	*0.02*	*0.48*	*17*	+	+	+
243	NC	Hexachlorocyclopentadiene	77-47-4	272.8	+	2.73	0.0075	0.03	22	+	+	+
244	*NC*	*8-Hydroxyquinoline*	*148-24-3*	*145.2*	+	*1.45*	*0.0058*	*0.04*	*42*	+	+	+
245	NC	4,4'-Isopropylidenediphenol	80-05-7	228.3	+	2.28	0.0912	0.4	43	+	+	+
246	NC	Lead dimethyldithiocarbamate	19010-66-3	447.6	+	4.48	0.000025	0.000056	18	+	+	+
247	NC	Lithocholic acid	434-13-9	376.6	+	3.77	0.56	1.5	17	+	+	-
248	NC	Malathion	121-75-5	330.4	+	3.30	<0.303	<0.92	18	+	+	+
249	*NC*	*Manganese(II) sulfate monohydrate*	*10034-96-5*	*169.0*	+	*1.69*	*0.18*	*1.065*	*18*	+	+	- (+)
250	NC	Methotrexate	59-05-2	454.4	+	4.54	0.001	0.0022	17	+	+	+
251	*NC*	*Methyl methacrylate*	*80-62-6*	*100.1*	+	*1.00*	*1.6*	*15.98*	*44*	-	-	-
252	NC	N-(1-Naphthyl)ethylenediamine 2HCl	1465-25-4	259.2	+	2.59	0.2	0.77	45	+	+	+
253	*NC*	*p-Nitroaniline*	*100-01-6*	*138.1*	+	*1.38*	*1.6*	*11.58*	*18*	-	-	-
254	*NC*	*4-Nitroanthranilic acid*	*619-17-0*	*182.1*	+	*1.82*	*2.2*	*12.08*	*22*	-	-	-
255	*NC*	*1-Nitronaphthalene*	*86-57-7*	*173.2*	+	*1.73*	*0.016*	*0.09*	*45*	+	+	+

256	NC	Penicillin VK	132-98-9	388.5	+	3.89	1.25	3.2	46	+	+	-
257	NC	*Phenol*	*108-95-2*	*94.1*	+	*0.94*	*2*	*21.25*	22	-	-	-
258	NC	*p-Phenylenediamine 2HCl*	*624-18-0*	*181.1*	+	*1.81*	*0.016*	*0.09*	45	+	+	+
259	NC	*1-Phenyl-2-thiourea*	*103-85-5*	*152.2*	+	*1.52*	*3*	*19.71*	22	-	-	-
260	NC	*Phthalic anhydride*	*85-44-9*	*148.1*	+	*1.48*	*1.48*	*10*	*38*	+	+	- (+)
261	NC	*Resorcinol*	*108-46-3*	*110.1*	+	*1.10*	*4*	*36.33*	22	-	-	-
262	NC	*Sodium chlorite*	*7758-19-2*	*90.4*	+	*0.90*	*0.02*	*0.22*	17	+	+	+
263	NC	Tetracycline HCl	64-75-5	480.9	+	4.81	0.01	0.02	17	+	+	+
264	NC	Tetraethylthiuram disulfide	97-77-8	296.5	+	2.97	5.00E-06	0.00002	22	+	+	+
265	NC	*Tetrakis(hydoxymethyl)phosphonium chloride*	*124-64-1*	*190.6*	+	*1.91*	*0.03*	*0.16*	22	+	+	+
266	NC	Tetrakis(hydoxymethyl)phosphonium sulphate	55566-30-8	251.2	+	2.51	0.005	0.02	44	+	+	+
267	NC	*Tin(II) chloride*	*7772-99-8*	*189.6*	+	*1.90*	*0.025*	*0.13*	22	+	+	+

C, Carcinogen; NC, Non-carcinogen; MW, Molecular weight; CA, Chromosomal aberration test; LEC, Lowest effective concentration; Equivalent to 10 mM means the equal concentration of weight per volume (mg/mL) to 10 mM.
+, Positive; −, Negative.
(+) shows positive after the application of the r-OECD TGfor the chemicals MW less than 200 (n = 46).
Italics means chemicals MW less than 200 (n = 142).
Highlight to the negative result by the re-evaluation.
[a] Current OECD test guideline adopted in 1997 (10 mM or 5 mg/mL whichever is lower).
[b] Draft revised OECD test guideline (10 mM or 2 mg/mL whichever is lower).
[c] ICH S2(R1) guideline (1 mM or 0.5 mg/mL whichever is lower).

approach, because there were no carcinogenicity data for nearly all the 124-CA positives from the JEC database. This approach consisted of the identification of effects from extreme culture conditions (*e.g.*, low pH, precipitation, cytotoxicity) and a review of the literature (*e.g.*, *in vivo* genotoxicity and carcinogenicity for the chemical, and for closely related chemicals). The level of concern for 'different' chemicals – to be used in human health-risk assessment – was defined and based on previously described analyses [9]. The general criteria were as follows: (1) negligible concern, negative result(s) in the *in vivo* genotoxicity or carcinogenicity test, clear evidence(s) of non-relevance (*e.g.*, extreme culture condition) for CA-induction and/or mode of action of the non-DNA target; (2) minimal concern, some evidence(s) of non-relevance of CA-induction or of an increasing level of negligible concern or negative result(s) in the *in vivo* genotoxicity tests with some limitations; (3) some concern, positive result(s) in the Ames test with negative result(s) or no data in the *in vivo* genotoxicity test, positive result(s) in the *in vivo* genotoxicity or carcinogenicity test in related chemicals or no supporting evidence(s) for reducing the level of concern; and (4) real concern, positive result(s) in the Ames or *in vivo* genotoxicity tests, or when mentioned in the list of IARC carcinogens in Group 2B or higher.

2.6. Distribution of the MWs of the chemicals

The distribution of the MWs of the 267 CA-positives from the CGX database and 124 CA-positives from the JEC database was investigated.

3. Results

3.1. Sensitivity and specificity analyses

Results from the re-evaluation of 267 CA-positive chemicals (210 carcinogens and 57 non-carcinogens) from the CGX database are shown in Table 1. The results of the sensitivity and specificity analyses on the 435 chemicals, including the 168 CA-negatives from the CGX database are shown in Table 3. In addition, 267 CA-positives in the original call of the CGX database included 19 positive chemicals (10 carcinogens, *i.e.*, CGX IDs 5, 65, 95, 116, 151, 153, 164, 187, 206, 208; and nine non-carcinogens, *i.e.*, CGX IDs 212, 215, 216, 251, 253, 254, 256, 259, 260) at more than 10 mM. The IARC Group-2A agents (probable carcinogens), acrylamide (CGX ID5), *N*-nitrosodiethylamine (CGX ID163) and urethane (CGX ID208) were also included in these 10 carcinogens. The number of CA-positive chemicals was reduced to 248, 248 or 176 from the 267 chemicals in the original call when the 1997-OECD, r-OECD or ICH TG was applied, respectively. Because these chemicals were considered negative, the number of CA-negative chemicals increased to 187, 187 or 259 from 168 in the original call by the application of the 1997-OECD, r-OECD or ICH TG, respectively. The sensitivity and specificity against carcinogenicity based on the re-evaluation for the 435 chemicals from the CGX database are shown in Table 3. The sensitivity was reduced to 63.1%, 63.1% or 45.4% from 66.2% based on the original call, and the specificity had increased to 59.3%, 59.3% or 72.9% from 51.7% based on the original call, by the application of the 1997-OECD, r-OECD or ICH TG, respectively. The application of the r-OECD TG did not affect the sensitivity and specificity of the application of the 1997-OECD TG. However, the application of the ICH TG reduced sensitivity and increased specificity by approximately 15%.

3.2. Analysis of the alteration of the number of CA-positives

The results of the re-evaluation of 124 CA-positives from the JEC database are shown in Table 2. Because the 124 CA-positives by the original call in the JEC database included six positive chemicals (*i.e.*, JEC IDs 2, 11, 87, 99, 106, 111) at more than 10 mM, 118 chemicals were considered positive under the 1997-OECD TG. Alterations in the number of positive chemicals are presented in Table 4. Application of r-OECD TG showed a small reduction in the number of CA-positives (113 out of 124 chemicals by 1997-OECD TG), but ICH TG reduced this number to approximately half (60 out of 124 chemicals). Moreover, the number of CA-positive chemicals decreased remarkably upon application of the ICH TG.

Table 2
Re-evaluation of chromosomal aberration test results on the 124 CA-positive chemicals from the JEC database, based on the different top-concentration limits in several test guidelines.

JEC ID	Chemical name	CAS No.	MW	CA (original call)	Equiv. to 10 mM (mg/mL)	LEC (mg/mL)	LEC (mM)	Ref.	1997-OECD[a]	r-OECD[b]	ICH[c]
									CA	CA	CA
1	*Acenaphthene*	*83-32-9*	*154.2*	+	*1.54*	*0.2*	*1.3*	*47*	+	+	- (+)
2	*o-Acetoacetotoluidine*	*93-68-5*	*191.2*	+	*1.91*	*2.5*	*13.1*	*47*	-	-	-
3	*3-Aminobenzenesulfonic acid*	*121-47-1*	*173.2*	+	*1.73*	*0.4*	*2.3*	*47*	+	+	- (+)
4	2-Amino-5-chloro-4-methylbenzenesulfonic acid	88-53-9	221.5	+	2.22	2.0	9.0	*47*	+	+	-
5	*N-(Aminoethyl)ethanolamine*	*111-41-1*	*104.2*	+	*1.04*	*1.0*	*9.6*	*47*	+	+	- (+)
6	*2-Amino-5-methylbenzenesulfonic acid*	*88-44-8*	*187.2*	+	*1.87*	*1.0*	*5.1*	*47*	+	+	- (+)
7	2-Amino-1-naphthalenesulfonic acid	81-16-3	223.3	+	2.23	1.1	4.9	*47*	+	+	-
8	*3-Aminophenol*	*591-27-5*	*109.1*	+	*1.09*	*0.03*	*0.3*	*47*	+	+	+
9	*4-Aminophenol*	*123-30-8*	*109.1*	+	*1.09*	*0.003*	*0.03*	*47*	+	+	+
10	*Azodicarbonamide*	*123-77-3*	*116.1*	+	*1.16*	*0.9*	*7.8*	*47*	+	+	- (+)
11	*Benzyltrimethylammonium chloride*	*56-93-9*	*185.7*	+	*1.86*	*1.9*	*10.2*	*47*	-	-	-
12	*4,4'-Biphenyldiol*	*92-88-6*	*186.2*	+	*1.86*	*0.03*	*0.2*	*47*	+	+	+
13	*1,3-Bis(aminomethyl)cyclohexane (mixtures of cis-, trans-)*	*2579-20-6*	*142.3*	+	*1.42*	*0.4*	*2.8*	*47*	+	+	- (+)
14	*1,2-Bis(2-chloroethoxy)ethane*	*112-26-5*	*187.1*	+	*1.87*	*0.06*	*0.3*	*47*	+	+	+
15	Bis(1-methylethyl)naphthalene	38640-62-9	212.3	+	2.12	0.14	0.7	*47*	+	+	+
16	1,3-Bis(2-methylphenyl)guanidine	97-39-2	239.3	+	2.39	0.6	2.5	*47*	+	+	-
17	*1-Bromo-3-chloropropane*	*109-70-6*	*157.4*	+	*1.57*	*0.3*	*1.6*	*47*	+	+	- (+)
18	N-*tert*-Butyl-2-benzothiazolesulfenamide	95-31-8	238.4	+	2.38	0.2	0.8	*47*	+	+	+
19	*tert-Butyl-methacrylate*	*585-07-9*	*142.2*	+	*1.42*	*0.4*	*2.8*	*47*	+	+	- (+)
20	*o-sec-Butylphenol*	*89-72-5*	*150.2*	+	*1.50*	*0.02*	*0.1*	*47*	+	+	+
21	*6-tert-Butyl-m-cresol*	*88-60-8*	*164.3*	+	*1.64*	*0.01*	*0.06*	*47*	+	+	+
22	*2-tert-Butylphenol*	*88-18-6*	*150.2*	+	*1.50*	*0.01*	*0.07*	*47*	+	+	+
23	*p-tert-Butylphenol*	*98-54-4*	*150.2*	+	*1.50*	*0.03*	*0.2*	*47*	+	+	+
24	Cadmium nitrate tetrahydrate	10022-68-1	308.5	+	3.09	0.01	0.02	*47*	+	+	+
25	*1-Chloro-2-(chloromethyl)benzene*	*611-19-8*	*161.0*	+	*1.61*	*0.1*	*0.6*	*47*	+	+	+
26	*4-Chloro-o-cresol*	*1570-64-5*	*142.6*	+	*1.43*	*0.1*	*0.7*	*47*	+	+	+
27	Chloropentabromocyclohexane	87-84-3	513.1	+	5.13	0.03	0.06	*47*	+	+	+
28	*2-Chlorophenol*	*95-57-8*	*128.6*	+	*1.29*	*0.3*	*2.3*	*47*	+	+	- (+)
29	*4-Chlorophenol*	*106-48-9*	*128.6*	+	*1.29*	*0.05*	*0.4*	*47*	+	+	+
30	Chromic acid disodium salt dihydrate	7789-12-0	297.8	+	2.98	0.001	0.003	*47*	+	+	+
31	C.I. Fluorescent brightner 271	41267-43-0	1347.1	+	13.47	5.0	3.7	*47*	+	-	-
32	*2,4-Diamino-6-phenyl-s-triazine*	*91-76-9*	*187.2*	+	*1.87*	*0.08*	*0.4*	*47*	+	+	+
33	1,4-Dibromobenzene	106-37-6	235.9	+	2.36	0.6	2.5	*47*	+	+	-
34	1,3-Dibromopropane	109-64-8	201.9	+	2.02	0.06	0.3	*47*	+	+	+
35	Dibutyl adipate	105-99-7	258.4	+	2.58	0.7	2.5	*47*	+	+	-
36	2-(Di-n-butylamino)ethanol	*102-81-8*	*173.3*	+	*1.73*	*0.3*	*1.7*	*47*	+	+	- (+)
37	2,6-Di-tert-butyl-4-ethylphenol	4130-42-1	234.4	+	2.34	0.045	0.19	*47*	+	+	+
38	2,4-Di-*tert*-butylphenol	96-76-4	206.3	+	2.06	0.01	0.05	*47*	+	+	+
39	*o-Dichlorobenzene*	*95-50-1*	*147.0*	+	*1.47*	*0.2*	*1.4*	*47*	+	+	- (+)
40	*3,4-Dichloro-1-butene*	*760-23-6*	*125.0*	+	*1.25*	*0.01*	*0.08*	*47*	+	+	+
41	*1,2-Dichloro-3-nitrobenzene*	*3209-22-1*	*192.0*	+	*1.92*	*0.1*	*0.6*	*47*	+	+	+
42	*1,4-Dichloro-2-nitrobenzene*	*89-61-2*	*192.0*	+	*1.92*	*0.15*	*0.8*	*47*	+	+	+
43	*α,4-Dichlorotoluene*	*104-83-6*	*161.0*	+	*1.61*	*0.0125*	*0.08*	*47*	+	+	+
44	*1,2-Dicyanobenzene*	*91-15-6*	*128.1*	+	*1.28*	*0.3*	*2.3*	*47*	+	+	- (+)
45	*Dicyclohexylamine*	*101-83-7*	*181.3*	+	*1.81*	*0.6*	*3.3*	*47*	+	+	- (+)
46	*N,N*-Dicyclohexyl-2-benzothiazolesulfenamide	4979-32-2	346.6	+	3.47	0.2	0.6	*47*	+	+	+
47	*2-(Diethylamino)ethyl methacrylate*	*105-16-8*	*185.3*	+	*1.85*	*0.6*	*3.2*	*47*	+	+	- (+)
48	*O,O'-Diethyl dithiophosphate*	*298-06-6*	*186.2*	+	*1.86*	*0.12*	*0.6*	*47*	+	+	+
49	*Diethyl fumarate*	*623-91-6*	*172.2*	+	*1.72*	*0.01*	*0.06*	*47*	+	+	+
50	*2-(Dimethylamino)ethyl acrylate*	*2439-35-2*	*143.2*	+	*1.43*	*0.05*	*0.3*	*47*	+	+	+

51	2-(Dimethylamino)ethyl methacrylate	2867-47-2	157.2	+	1.57	0.6	3.8	47	+	+	- (+)
52	2,3-Dimethylaniline (2,3-Xylidine)	87-59-2	121.2	+	1.21	0.6	5.0	47	+	+	- (+)
53	2,6-Dimethylaniline (2,6-Xylidine)	87-62-7	121.2	+	1.21	0.3	2.5	47	+	+	- (+)
54	3,5-Dimethylaniline (3,5-Xylidine)	108-69-0	121.2	+	1.21	0.9	7.4	47	+	+	- (+)
55	N,N-Dimethylbenzylamine	103-83-3	135.2	+	1.35	0.4	3	47	+	+	- (+)
56	N-(1,3-Dimethylbutyl)-N'-phenyl-p-phenylenediamine	793-24-8	268.4	+	2.68	0.005	0.02	47	+	+	+
57	2,4-Dinitrophenol	51-28-5	184.1	+	1.84	1.2	6.5	47	+	+	- (+)
58	Diphenyl cresyl phosphate	26444-49-5	340.3	+	3.40	0.04	0.1	47	+	+	+
59	Disperse Red 206	26630-87-5	580.1	+	5.80	2.5	4.3	47	+	-	-
60	Disperse Yellow 42	5124-25-4	369.4	+	3.69	0.08	0.2	47	+	+	+
61	2,3-Epoxypropyl methacrylate	106-91-2	142.2	+	1.42	0.02	0.1	47	+	+	+
62	Ethenyltrimethoxysilane	2768-02-7	148.2	+	1.48	0.8	5.4	47	+	+	- (+)
63	4-Ethoxybenzeneamine (p-Phenetidin)	156-43-4	137.2	+	1.37	0.05	0.4	47	+	+	+
64	N-Ethylaniline	103-69-5	121.2	+	1.21	1.1	9.1	47	+	+	- (+)
65	2-Ethylanthraquinone	84-51-5	236.3	+	2.36	0.16	0.6	47	+	+	+
66	2-Ethylbutyric acid	88-09-5	116.2	+	1.16	0.4	3.4	47	+	+	- (+)
67	3-Ethylphenol	620-17-7	122.2	+	1.22	0.05	0.4	47	+	+	+
68	4-Ethylphenol	123-07-9	122.2	+	1.22	0.04	0.3	47	+	+	+
69	Ferrous sulfate heptahydrate	7782-63-0	278.0	+	2.78	0.5	1.8	47	+	+	-
70	Glycerol triacetate	102-76-1	218.2	+	2.18	2.2	10.0	47	+	-	-
71	Hydrazine monohydrate	7803-57-8	50.1	+	0.50	0.06	1.2	47	+	+	- (+)
72	2-Hydroxybenzaldehyde	90-02-8	122.1	+	1.22	0.1	0.8	47	+	+	+
73	4-Hydroxy-benzenesulfonic acid, tin (2+) tetrahydride	70974-33-3	465.1	+	4.65	0.528	1.1	47	+	+	-
74	4-Hydroxybenzoic acid	99-96-7	138.1	+	1.38	0.7	5.1	47	+	+	- (+)
75	2-Hydroxyethyl methacrylate	868-77-9	130.2	+	1.30	0.7	5.4	47	+	+	- (+)
76	3-Hydroxy-2-naphthalenecarboxylic acid	92-70-6	188.2	+	1.88	0.75	4.0	49	+	+	- (+)
77	2-Hydroxypropanenitrile	78-97-7	71.1	+	0.71	0.7	10.0	47	+	+	- (+)
78	2-Mercaptobenzimidazole	583-39-1	150.2	+	1.50	0.8	5.3	47	+	+	- (+)
79	Methacrylic acid, monoester with propane-1,2-diol	27813-02-1	144.2	+	1.44	0.7	4.9	47	+	+	- (+)
80	(Methacryloyloxyethyl)trimethylammonium chloride	5039-78-1	207.7	+	2.08	2.1	10.0	47	+	-	-
81	Methacrylonitrile (Methyl Acrylonitrile)	126-98-7	67.1	+	0.67	0.07	1.0	47	+	+	+
82	3-Methoxybenzeneamine	536-90-3	123.2	+	1.23	0.8	6.5	47	+	+	- (+)
83	Methoxymethanol	4461-52-3	62.1	+	0.62	0.02	0.3	47	+	+	+
84	1-Methoxynaphthalene	2216-69-5	158.2	+	1.58	0.02	0.1	47	+	+	+
85	Methyl acetoacetate	105-45-3	116.1	+	1.16	1.2	10.0	47	+	+	- (+)
86	N-Methylaniline	100-61-8	107.2	+	1.07	0.6	5.6	47	+	+	- (+)
87	3-Methylbenzoic acid	99-04-7	136.2	+	1.36	1.5	11.0	47	-	-	-
88	4-Methylbenzoic acid	99-94-5	136.2	+	1.36	1.2	8.8	47	+	+	- (+)
89	4,4'-Methylenebis(2-chloroaniline)	101-14-4	267.2	+	2.67	0.04	0.1	47	+	+	+
90	Methylenediphenol	1333-16-0	200.2	+	2.00	0.01	0.05	47	+	+	+
91	4,4'-Methylenediphenol	620-92-8	200.2	+	2.00	0.2	1.0	47	+	+	+
92	4-(1-Methylethenyl)phenol	4286-23-1	134.2	+	1.34	0.06	0.4	47	+	+	+
93	Methyl isothiocyanate	556-61-6	73.1	+	0.73	0.003	0.03	47	+	+	+
94	3-Methyl-4-nitrophenol	2581-34-2	153.2	+	1.53	0.04	0.3	47	+	+	+
95	3-Methylphenol (m-Cresol)	108-39-4	108.1	+	1.08	0.03	0.3	47	+	+	+
96	2-(4-Morpholinyldithio)benzothiazole	95-32-9	284.4	+	2.84	0.1	0.3	47	+	+	+
97	1-Naphthylacetic acid	86-87-3	186.2	+	1.86	1.7	9.1	47	+	+	- (+)
98	4-Nitro-o-anisidine	97-52-9	168.2	+	1.68	0.08	0.5	47	+	+	+
99	3-Nitrobenzenamine	99-09-2	138.1	+	1.38	1.6	11.6	47	-	-	-
100	p-Nitrophenol sodium salt	824-78-2	161.1	+	1.61	0.6	3.7	47	+	+	- (+)
101	4,4'-Oxybis(benzenesulfonylhydrazide)	80-51-3	358.4	+	3.58	0.6	1.7	47	+	+	-
102	2-Pentylanthraquinone	13936-21-5	278.4	+	2.78	0.06	0.2	47	+	+	+
103	N-Phenylmaleimide	941-69-5	173.2	+	1.73	0.01	0.02	47	+	+	+
104	N-Phenyl-N'-isopropyl-p-phenylenediamine	101-72-4	226.3	+	2.26	0.01	0.01	47	+	+	+
105	Phosphoric acid, dodecyl ester, sodium salt	50957-96-5	288.3	+	2.88	0.05	0.16	47	+	+	+

Table 2 (*Continued*)

JEC ID	Chemical name	CAS No.	MW	CA (original call)	Equiv. to 10 mM (mg/mL)	LEC (mg/mL)	LEC (mM)	Ref.	1997-OECD[a]	r-OECD[b]	ICH[c]
									CA	CA	CA
106	*Phthalimide*	*85-41-6*	*147.1*	+	*1.47*	*2.5*	*17.0*	*47*	-	-	-
107	Sorbitan monooctadecanoate	1338-41-6	430.6	+	4.31	1.1	2.5	47	+	+	-
108	4,4'-Sulfonyldiphenol	80-09-1	250.3	+	2.50	0.4	1.6	47	+	+	-
109	*3a,4,7,7a-Tetrahydro-1H-indene*	*3048-65-5*	*120.2*	+	*1.20*	*0.004*	*0.8*	*47*	+	+	+
110	2,3,4,4'-Tetrahydroxybenzophenone	31127-54-5	246.2	+	2.46	0.0148	0.06	47	+	+	+
111	*2,2,6,6-Tetramethyl-4-hydroxypiperidine*	*2403-88-5*	*157.3*	+	*1.57*	*2.0*	*12.7*	*47*	-	-	-
112	*Thiourea dioxide*	*4189-44-0*	*108.1*	+	*1.08*	*0.6*	*5.5*	*47*	+	+	- (+)
113	*Thymol*	*89-83-8*	*150.2*	+	*1.50*	*0.002*	*0.01*	*47*	+	+	+
114	*Tolylene diisocyanate (Toluene diisocyanate)*	*26471-62-5*	*174.2*	+	*1.74*	*0.3*	*1.8*	*47*	+	+	- (+)
115	2,4,6-Tribromophenol	118-79-6	330.8	+	3.31	0.05	0.2	47	+	+	+
116	*1,3,5-Trihydroxybenezene*	*108-73-6*	*126.1*	+	*1.26*	*0.1*	*1.0*	*47*	+	+	+
117	*2,4,6-Trimercapto-S-triazine*	*638-16-4*	*177.3*	+	*1.77*	*0.8*	*4.5*	*47*	+	+	- (+)
118	*Trimethoxyphosphine*	*121-45-9*	*124.1*	+	*1.24*	*1.2*	*10.0*	*47*	+	+	- (+)
119	*Trimethylamine*	*75-50-3*	*59.1*	+	*0.59*	*0.4*	*6.8*	*47*	+	+	- (+)
120	*2,3,6-Trimethylphenol*	*2416-94-6*	*136.2*	+	*1.36*	*0.05*	*0.4*	*47*	+	+	+
121	2,4,6-Trinitrophenol (Picric acid)	88-89-1	229.1	+	2.29	1.6	7.0	47	+	+	-
122	Triphosphoric acid aluminium salt	13939-25-8	317.9	+	3.18	2.0	6.3	47	+	+	-
123	1,3,5-Tris(3,5-di-*tert*-butyl-4-hydroxybenzyl)isocyanuric acid	27676-62-6	784.1	+	7.84	2.5	3.2	47	+	-	-
124	*2-Vinylpyridine*	*100-69-6*	*105.2*	+	*1.05*	*0.01*	*0.1*	*47*	+	+	+

MW, Molecular weight; CA, Chromosomal aberration test; LEC, Lowest effective concentration;
Equivalaent to 10 mM means the equal concentration of weight per volume (mg/mL) to 10 mM.
+, positive; –, negative.
(+) shows positive after the appication of the r-OECD TG for the chemicals MW less than MW 200 (n = 41).
Italics means chemicals MW less than 200 (n = 85).
Highilight to the negative result by the re-evaluation.

[a] Current OECD test guideline adopted in 1997 (10 mM or 5 mg/mL whichever is lower)

[b] Draft revised OECD test guideline (10 mM or 2 mg/mL whichever is lower)

[c] ICH S2(R1) guideline (1 mM or 0.5 mg/mL whichever is lower);

Table 3
Sensitivity and specificity for carcinogenicity upon application of each test guideline for the dataset on 435 chemicals from the CGX database.

Test guideline	Dataset	CA-negative	CA-positive	Total	Calculation
Original call[a]	Carcinogen	107	210	317	Sensitivity, 66.2% (210/317)
	Non-carcinogen	61	57	118	Specificity, 51.7% (61/118)
	Total	168	267	435	
1997-OECD[b]	Carcinogen	117	200	317	Sensitivity, 63.1% (200/317)
	Non-carcinogen	70	48	118	Specificity, 59.3% (70/118)
	Total	187	248	435	
r-OECD[c]	Carcinogen	117	200	317	Sensitivity, 63.1% (200/317)
	Non-carcinogen	70	48	118	Specificity, 59.3% (70/118)
	Total	187	248	435	
ICH[d]	Carcinogen	173	144	317	Sensitivity, 45.4% (144/317)
	Non-carcinogen	86	32	118	Specificity, 72.9% (86/118)
	Total	259	176	435	
ICH (modified)[e]	Carcinogen	133	184	317	Sensitivity, 58.0% (184/317)
	Non-carcinogen	80	38	118	Specificity, 67.8% (80/118)
	Total	213	222	435	

[a] Call in CGX database [16], including 19 CA-positives (10 carcinogens and 9 non-carcinogens) at >10 mM.
[b] Current OECD test guideline adopted in 1997 (10 mM or 5 mg/mL whichever is lower).
[c] Draft revised OECD test guideline (10 mM or 2 mg/mL whichever is lower).
[d] ICH S2(R1) guideline (1 mM or 0.5 mg/mL whichever is lower).
[e] Applied to the r-OECD TG for the chemicals MW less than 200.

3.3. Evaluation of the relevance of in vitro CA results

Fifty-three chemicals showed different results between r-OECD and ICH TGs (*i.e.*, positive call and negative call, respectively) (Table 2). Thus, these 53 different chemicals were detected as positive in the *in vitro* CA test with r-OECD TG but not with the ICH TG, indicating that the 53 chemicals would be missed if the ICH TG had been used. The relevance of the *in vitro* CA results was evaluated on the basis of the weight-of-evidence approach, and the level of concern on "different" chemicals was defined.

The 53 different chemicals included 34 chemicals that had their appropriate levels of concern evaluated in our previous study (four of 'some concern', seven of 'minimal concern', and 23 of 'negligible concern') [9]. All 34 chemicals were negative in the Ames test [9,47].

The remaining 19 chemicals were evaluated as a new level of concern. Fifteen out of the 19 chemicals were positive in the Ames test. To reveal the weight of the Ames-positives, the *in vivo* genotoxicity and carcinogenicity assays were reviewed for the 15 chemicals (Table 5). Seven of these, *i.e.*, *N*-(aminoethyl)ethanolamine (JEC ID5), azodicarbonamide (JEC ID10), 2-(dimethylamino)ethyl methacrylate (JEC ID51), 2,6-dimethylaniline (JEC ID53), 4,4′-oxybis(benzenesulfonylhydrazide) (JEC ID101), tolylene diisocyanate (JEC ID114) and 2,4,6-trinitrophenol (JEC ID121), were negative in the *in vivo* micronucleus (MN) test [47,49,50]. However, two (JECD IDs 53 and 114) were categorized in the IARC Group 2B (possible human carcinogen) [50]. Two other chemicals, hydrazine monohydrate (JEC ID71) and 3-methoxybenzeneamine (JEC ID82), were positive in the *in vivo* MN test [47,50]; the former chemical (JEC ID71) was categorized in IARC's Group 2B [50]. No *in vivo* genotoxicity and/or carcinogenicity data were available for the remaining six chemicals. On the basis of these data, four chemicals (JEC IDs 53, 71, 82 and 114) can be considered to be of real concern as a possible human carcinogen or an *in vivo* genotoxin. Genotoxic effects could not be ruled out for Ames-positive chemicals, despite the negative results obtained in an *in vivo* MN test. Thus, the remaining 11 chemicals (five *in vivo* MN-negatives and six without *in vivo* genotoxicity data) were considered to be of some concern.

For the last four chemicals, two (JEC IDs 76 and 117) were of negligible concern, one (JEC ID1) was of minimal concern, and one (JEC ID73) was of some concern on the basis of the following evaluations:

JEC ID 1. Acenaphthene (CAS No. 83-32-9): Acenaphthene induced CAs (16.4%, 195 cells analyzed) at the highest concentration of 0.20 mg/mL (1.3 mM) only with S9-mix; the relative cell growth, as measured by monolayer confluence, was 28.0%. A lower concentration of 0.10 mg/mL showed a CA frequency of 4.5%, with 30.0% relative cell growth [47]. In a bacterial reverse-mutation assay (*i.e.*, Ames test), acenaphthene was negative with or without S9. No *in vivo* genotoxicity data were available. The data did not explain that the CAs observed *in vitro* were irrelevant due to their high toxicity. Acenaphthene was classified in Group 3 by IARC due to inadequate evidence in experimental animals for its carcinogenicity [50]. There was insufficient evidence to classify this finding as a negligible level of concern; thus, we concluded that it fell in the category of a minimal level of concern.

JEC ID 73. 4-Hydroxy-benzenesulfonic acid, tin (2+) tetrahydride (CAS No. 70974-33-3): 4-Hydroxy-benzenesulfonic acid, tin (2+) tetrahydride induced CAs (4.5%, 12.5% or 24.0% at 0.528 mg/mL (1.1 mM), 0.755 mg/mL or 1.078 mg/mL, respectively) after 6-h treatment without S9; the relative cell growth, as measured by ATP contents, was 85%, 64% or 53% [47]. With S9, CAs (14.0%) were induced at 2.2 mg/mL after 6-h treatment; the relative cell growth was 43%. Precipitation was observed at the end of the treatment period with S9. The Ames test provided negative results, with or without the S9 mix [47]. No *in vivo* genotoxicity data were available. There was no supporting evidence for a reduced level of concern, and thus some concern remains.

Table 4
Alterations of the number of 124 CA-positives from the JEC database after the application of each test guideline.

Dataset	Original call[a]	1997-OECD[b]	r-OECD[c]	ICH[d]	ICH (modified)[e]
JEC 124 CA-positives	124	118	113	60	101

[a] Call in JEC database [47], including 6 CA-positives) at >10 mM.
[b] Current OECD test guideline adopted in 1997 (10 mM or 5 mg/mL whichever is lower).
[c] Draft revised OECD test guideline (10 mM or 2 mg/mL whichever is lower).
[d] ICH S2(R1) guideline (1 mM or 0.5 mg/mL whichever is lower).
[e] Applied to the r-OECD TG for the chemicals MW less than 200.