Supplementary Table 1. Summary of the data used for analysis of weight of evidence in support of the AOP.[1].

Key Event	Model	Chemicals	Endpoint	Response	Reference
MIE: binding to tubulin	In vitro system (Bovine and chicken brain)	Colchicine	Colchicine binding to tubulin	Colchicine binds to a limited number of soluble tubulin dimers, then the colchicine-dimer complex binds to microtubule end preventing addition of new dimers.	[Margolis and Wilson 1977]
MIE: binding to tubulin	In vitro system (Bovine brain)	Colchicine	Stoichiometry of colchicine binding	50% inhibition of assembly occurs when the stoichiometry of colchicine-dimer complex bound per microtubule assembly end is ~0.5. Colchicine-bound dimers at the assembly end dissociate significantly more slowly than drug-free dimers.	[Margolis et al. 1980]
MIE: binding to tubulin	In vitro system (Rat brain)	Colchicine, podophyllotoxin	Biochemical characterization of colchicine and podophyllotoxin binding to tubulin.	Association rate constant for podophillotoxin binding is 3.8 x10^{6} M^{-1} h^{-1}, ~10 times higher than colchicine. Activation energies for binding are 14.5 kcal/mol for podophillotoxin and 20.3 kcal/mol for colchicine. This study shows that colchicine and podophyllotoxin share a common binding site on tubulin but also have unique ones.	[Cortese et al. 1977]
MIE: binding to tubulin	Biochemical assay	Colchicine	Biochemical characterization	Mammalian tubulin binds colchicine with an average affinity constant of 10^{-6} to 10^{-7} M^{-1} at 37 °C. The half-life of the binding site is up to 7.5 h. Kinetics of colchicine binding is a two-step reaction in which a rapid pre-equilibrium is followed by a slow, poorly reversible unimolecular step.	[Hastie 1991; Bhattacharyya et al. 2008]
MIE: binding to tubulin	In vitro system (Rat brain)	Colchicine	Characterization of binding site on tubulin	At least two regions of β-tubulin are involved in colchicine binding and the span of the colchicine molecule (<11 Å) bridges these two regions.	[Uppuluri et al. 1993]
MIE: binding to tubulin	Sea urchin (Unfertilized eggs)	Colchicine	Colchicine-binding activities of highly purified tubulin	Affinity constant determined at different temperature (between 8 and 30 °C) and between egg tubulin and sperm tail tubulin. The affinity constant of egg tubulin (3.48 x10^{5} liter/mol) is 5-fold lower than that of sperm tubulin.	[Wilson et al. 1984]

[1] Research articles providing data for more than one Key Event are listed in each one of the appropriate sections. Abbreviations: APC = Anaphase Promoting Complex; GVBD = Germinal Vesicle Breakdown; HCG = Human Chorionic Gonadotropin; KE = Key Event; MTOC = Microtubule-Organizing Centers;Plk1 = Polo-like kinase-1.

KE1: Disruption of microtubule dynamics	Human (germinal vesicle stage oocytes)	In vitro culture for 24 h in the presence of colchicine	Spindle formation	In the colchicine group, microtubules polymerization is inhibited and meiotic spindle does not form.	[Liu et al. 2010]
KE1: Disruption of microtubule dynamics	Sea urchin (Embryos)	Colchicine and colcemid.	Association and dissociation rates of tubulin to microtubules	After addition of colchicine at concentrations of 0.1-3.0 mM microtubule polymerization decreased rapidly and simultaneously throughout the central spindle and aster.	[Salmon et al. 1984]
KE2: Spindle disorganization	Mouse (Oocytes)	Colcemid	Induction of enucleation in activated oocytes	After in vitro treatment with 0.4 µg/mL (1 µM) reduction of spindle size and lower microtubule density is detected in activated oocytes with respect to controls; cytoskeleton remodelling is also observed.	[Ibanez et al. 2003]
KE2: Spindle disorganization	Mouse (Oocytes)	Nocodazole	Spindle assembly and meiotic progression	In vitro exposure of oocytes to 20 µg/mL (67 µM) causes a gradual disassembly of spindle, which is completed within 15 min.	[Xu et al. 2012]
KE2: Spindle disorganization	Mouse (Oocytes)	Colchicine	Cellular localization of Aurora A	Aurora A normally localizes to the spindle poles of the meiotic spindle from metaphase I to metaphase II. In the presence of colchicine (25 µM), this localization does not occur.	[Yao et al. 2004]
KE2: Spindle disorganization	Pig (Oocytes)	Colchicine	Cellular localization of Polo-like kinase-1	Plk1 normally localizes to the spindle poles of the meiotic spindle at the beginning of metaphase and then translocates to the middle region. At anaphase and telophase, Plk1 concentrates in the midbody of cytoplasmic cleavages. Plk1 disappears at the spindle region when microtubule formation is inhibited by colchicine (25 µM).	[Yao et al. 2003]
KE2: Spindle disorganization	Mouse (Oocytes)	Colchicine	Cellular localization of Polo-like kinase-1	Plk1 disappears from the spindle region when microtubule formation is inhibited by colchicine (25 µM).	[Tong et al. 2002]
KE2: Spindle disorganization	Mouse (Oocytes)	Colchicine	Cellular localization of GTPase Ran	During completion of meiosis I and II, Ran concentrates to the meiotic spindle microtubules except for the midbody region. Ran concentration around the spindle disappears when microtubule assembly is inhibited by colchicine (25 µM).	[Cao et al. 2005]

KE3: Altered chromosome dynamics	Mouse (Oocytes)	2-methoxyestradiol (3.75 µM, 9 or 10 h exposure).	Spindle morphology and chromosome congression	After in vitro exposure, bipolar spindle formation and chromosome alignment at the metaphase plate are severely disturbed in oocytes. 6 hours later, the percentage of aneuploid oocytes is significantly increased above the control level (described in KE4).	[Eichenlaub-Ritter et al. 2007]
KE3: Altered chromosome dynamics	Mouse (Oocytes)	Nocodazole (20, 30, 40 nM, 13 h exposure)	Spindle morphology and chromosome congression	All tested concentrations induce spindle abnormalities in vitro. The lowest effective concentration for chromosome congression defects is 40 nM. The dose-response relationships are congruent with the proposed AOP.	[Shen et al. 2005]
KE3: Altered chromosome dynamics	Mouse (Oocytes)	-	Disregulation of spindle assembly and chromosome congression as a function of Bub1 activity	In the absence of Bub1 function chromosome congression is defective and causes chromosome mis-segregation during the first meiotic division (see KE4).	[McGuinness et al. 2009]
KE3: Altered meiotic chromosome dynamics	Mouse (Oocytes)	-	Disregulation of spindle assembly and chromosome congression as a function of an MTOC-associated protein concentration.	Depletion of a MTOC component increases the incidence of spindle and chromosome congression abnormalities from 20 to 74% and from 10 to 75% respectively.	[Ou et al. 2010]
KE3: Altered meiotic chromosome dynamics	Mouse (Oocytes)	-	Timing of chromosome congression from APC activation to anaphase onset	At the time of APC-induced cyclin B1 degradation about 30% of oocytes carry non-aligned chromosomes. Non-congressed bivalents do not influence the timing of anaphase onset (thus excluding further SAC action). Live-imaging indicates that non-aligned bivalents may persist for several hours during the time interval separating APC activation and anaphase onset. Furthermore, evidence of bivalents departing from the equatorial plane is provided, strengthening the plasticity of events occurring at the metaphase I/anaphase I transition in oocytes.	[Lane et al. 2012]
KE4: Altered chromosome number	Chinese hamster (Oocytes)	Colchicine (3 mg/kg i.p.; ~10 h before ovulation)	Aneuploidy in metaphase II oocytes: hyperhaploidy	Ten-fold significant increase of hyperhaploid oocytes. 8.6% (30/342) hyperhaploid oocytes vs 0.8% (14/1730) in controls. Oocytes collected after natural ovulation, strengthening the relevance of data for human hazard assessment.	[Sugawara and Mikamo 1980]

KE4: Altered chromosome number	Djungarian haster (Oocytes)	Colchicine (3 mg/kg i.p.; 5 h after HCG)	Aneuploidy in metaphase II oocytes: hyperhaploidy	Significant increase of hyperhaploid oocytes. 11.7% (16/137) hyperhaploid oocytes vs 3.5 (4/113) in controls.	[Hummler and Hansmann 1985]
KE4: Altered chromosome number	Mouse (Oocytes)	Colchicine (0.25 mg/kg i.p.; 3 h after HCG)	Aneuploidy in metaphase II oocytes: hyperhaploidy	Significant increase of hyperhaploid oocytes, in both young and old mice. 11.2% (27/241) hyperhaploid oocytes vs 0.4% (1/232) in controls, for young mice (9-12 weeks of age). 15.6% (12/77) hyperhaploid oocytes vs. 2.3 (4/174) in controls, for old females (50-60 weeks of age).	[Tease and Fisher 1986]
KE4: Altered chromosome number	Mouse (Oocytes)	Colchicine (0.2 mg/kg; administered i.p. around the time of HCG (-4 h to + 4 h).	Aneuploidy in metaphase II oocytes: hyperhaploidy	Significant increases of hyperhaploid oocytes at all time points investigated. The percentages of hyperhaploid oocytes were 0.8 (4/520), 2.6 (16/625), 5.7 (29/508), 7.8 (36/462), 3.5 (17/480) and 2.7 (11/407) for controls, +4, +2, 0, -2 and -4 hr pre/post HCG, respectively. The study shows that in preovulatory oocytes the sensitivity window for aneuploidy induction by colchicine is at least 8h long.	[Mailhes and Yuan 1987]
KE4: Altered chromosome number	Mouse (Oocytes)	Colchicine: 0.1, 0.2, 0.3 mg/kg; administered i.p. at the time of HCG.	Aneuploidy in metaphase II oocytes: hyperhaploidy	Dose-related increase in hyperhaploid oocytes. The percentages of hyperhaploid oocytes were 1.2 (2/167), 0.5 (1/182), 9.5 (21/220), and 18.8 (38/202) for controls, 0.1, 0.2, and 0.3 mg/kg, respectively. The Lowest Effective Tested Dose is 0.2 mg/kg.	[Mailhes et al. 1988]
KE4: Altered chromosome number	Mouse (Oocytes)	Colchicine: 0.2, 0.3, 0.4 0 mg/kg by i.p. and 1.0, 2.0, 3.0, 4.0 mg/kg by gavage; administered at the time of HCG.	Aneuploidy in metaphase II oocytes: hyperhaploidy	Dose-dependent significant increases of hyperhaploid oocytes after both i.p and oral administration. After i.p. administration, the percentages of hyperhaploid oocytes were 0.2 (1/606), 7.3 (37/504), 20.8 (152/731), and 23.5 (75/319) for controls, 0.2, 0.3, and 0.4 mg/kg, respectively. After oral administration, the percentages of hyperhaploid oocytes were 1.4 (3/216), 1.5 (8/539), 15.9 (81/511), 17.8 (71/398), and 25.1 (98/391) for controls, 1.0, 2.0, 3.0, and 4.0 mg/kg, respectively. An aneuploidy induction effectiveness ratio of 10 is observed between oral and i.p doses.	[Mailhes et al. 1990]

KE4: Altered chromosome number	Mouse (Oocytes)	2-methoxyestradiol (1.25, 2.5, 3.75, 5, 7.5 µM, 16 h exposure).	Aneuploidy in metaphase II oocytes: hyperhaploidy	Dose-related increases in hyperhaploid oocytes after in vitro treatment. The percentages of hyperhaploid oocytes were 0.5 (1/219), 0.0 (0/113), 1.4 (2/142), 6.0 (6/105), 23.5 (23/100), and 100.0 (6/6) for controls, 1.25, 2.5, 3.75, 5 and 7.5 µM, respectively. The lowest effective tested concentration was 3.75 µM. This paper provides evidence that spindle and chomosome congression defects precede the observation of aneuploid oocytes (see KE3 section of this Table).	[Eichenlaub-Ritter et al. 2007]
KE4: Altered chromosome number	Chinese hamster (Oocytes)	Podophyllotoxin (20 mg/kg i.p., at the onset of the first meiotic spindle formation, i.e.16 h before oocyte harvest).	Aneuploidy in metaphase II oocytes: hyperhaploidy	Statistically significant increase in hyperhaploid oocytes. The percentages of hyperhaploid oocytes were 1.5 (3/198) and 40.3 (62/154) for controls and 20 mg/kg, respectively.	[Tateno et al. 1995]
KE4: Altered chromosome number	Mouse (Oocytes)	Nocodazole (10 µM, 1 h exposure during first meiotic spindle formation).	Aneuploidy in metaphase II oocytes: hyperhaploidy	Statistically significant increase in hyperhaploid oocytes after in vitro treatment. The percentages of hyperhaploid oocytes were 1.7 (3/176) and 8.6 (5/58) for controls and 10 µM, respectively.	[Eichenlaub-Ritter and Boll 1989]
KE4: Altered chromosome number	Mouse (Oocytes)	Nocodazole (20, 30, 40 nM, 16 h exposure).	Aneuploidy in metaphase II oocytes: hyperhaploidy	Dose-dependent increases of hyperhaploid oocytes after in vitro treatment. The percentages of hyperhaploid oocytes were 0.9 (1/108), 0.0 (0/139), 2.8 (4/142), and 10.0 (16/160) for controls, 20, 30, and 40 nM, respectively. The lowest effective concentration for aneuploidy induction in metaphase II is 40 nM. This paper provides evidence of aneuploidy linked to evidence of spindle and chromosome congression defects (see KE3 section of this Table), with dose response relationships congruent with the proposed AOP.	[Shen et al. 2005]

KE4: Altered chromosome number	Mouse (Oocytes)	Nocodazole (20, 30, 40 nM, 16 h exposure).	Aneuploidy in metaphase II oocytes: hyperhaploidy	Dose-dependent increases of hyperhaploid oocytes after in vitro treatment. The percentages of hyperhaploid oocytes were 0.0 (0/105), 3.9 (5/129), 12.2 (12/98), and 22.7 (5/22) for controls, 20, 30, and 40 nM, respectively. The lowest effective tested concentration is 30 nM. Oocytes enclosed in their follicles appear more sensitive than denuded oocytes.	[Sun et al. 2005]
KE4: Altered chromosome number	Mouse (Oocytes)	Nocodazole (100 nM, 14-18 h exposure).	Aneuploidy in metaphase II oocytes: hyperhaploidy	Significant induction of hyperhaploidy when in vitro exposure of GVBD oocytes start within 6 h after follicle release.	[Everett and Searle 1995]
KE4: Altered chromosome number	Mouse (Oocytes)	Nocodazole (35, 70 mg/kg i.p.; administered at the time of HCG).	Aneuploidy in metaphase II oocytes: hyperhaploidy	Hyperhaploidy is significantly increased at 70 mg/kg. The percentages of hyperhaploid oocytes were 0.0 (0/230), 0.0 (0/194) and 7.3 (8/110) for controls, 35 and 70 mg/kg, respectively. The lowest effective dose roughly corresponds to an in vitro concentration of 230 µM, much higher than active concentrations on cultured oocytes. Poor water solubility and limited bioavailability of nocodazole after i.p. treatment likely account for this difference.	[Sun et al. 2005]
KE4: Altered chromosome number	Mouse (Oocytes)	Benomyl (500, 1000, 1500, 1750, 2000 mg/kg p.o.; administered at the time of HCG).	Aneuploidy in metaphase II oocytes: hyperhaploidy	Hyperhaploidy is significantly increased at all doses tested. The percentages of hyperhaploid oocytes were 0.3 (1/309), 3.9 (6/155), 16.6 (38/229), 35.4 (46/130), 27.9 (60/215) and 29.4 (42/143) for controls, 500, 1000, 1500, 1750 and 2000 mg/kg, respectively. A saturation of the effect is detected for doses above 1500 mg/kg, but its cause is not investigated.	[Mailhes and Aardema 1992]
KE4: Altered chromosome number	Djungarian hamster (Oocytes)	Carbendazim (1000 mg/kg p.o.; administered 4.5 or 6 h after HCG).	Aneuploidy in metaphase II oocytes: hyperhaploidy	Significant increases of hyperhaploidy, with decreased effect at later treatment time. The percentages of hyperhaploid oocytes were 40.6 (26/64) and 22.5 (18/80) for +4.5 and +6.5 after HCG, respectively. Differential involvement of specific chromosomes at each treatment time suggests asynchronous segregation of bivalents in this species.	[Hummler and Hansmann 1988]

KE4: Altered chromosome number	Syrian hamster (Oocytes)	Carbendazim (1000 mg/kg p.o.; administered ~13 h before ovulation).	Hyperhaploidy. Preimplantation embryonic development.	About 4-fold increase of hyperhaploid oocytes over the control value. The percentages of hyperhaploid oocytes were 7.7 (4/52) and 27.2 (33/121) for controls and 1000 mg/kg, respectively. Delayed preimplantation embryonic development and decreased implantation rate in treated animals suggest a post-fertilization consequence of aneuploidy in oocytes.	[Jeffay et al. 1996]
KE4: Altered chromosome number	Mouse (Oocytes)	Thiabendazole (50, 100, 150 mg/kg i.p.; administered at the same time of HCG)	Aneuploidy in metaphase II oocytes: hyperhaploidy	Small but significant increase of hyperhaploid oocytes at 100 mg/kg. The percentages of hyperhaploid oocytes were 0 (0/472), 0.5 (2/410), 1.3 (6/478), and 0.7 (3/427), for controls, 50, 100 and 150 mg/kg, respectively. TBS significantly reduced the proportion of ovulatory mice and the number of oocytes collected per ovulatory female.	[Mailhes et al. 1997]
KE4: Altered chromosome number	Mouse (Oocytes)	Vinblastine (0.09, 0.23, 0.45, 0.9, 4.5, 9 mg/kg i.p.; administered at the time of HCG)	Aneuploidy in metaphase II oocytes: hyperhaploidy	Dose-dependent significant increases of hyperhaploid oocytes at 0.23 mg/kg and 0.45 mg/kg. The percentages of hyperhaploid oocytes were 0.9 (2/219), 0.9 (1/111), 17.2 (26/151), and 59.7 (40/67), for controls, 0.09, 0.23, and 0.45 mg/kg, respectively. At higher doses almost all oocytes are arrested at the metaphase I stage.	[Russo and Pacchierotti 1988]
KE4: Altered chromosome number	Mouse (Oocytes)	Vinblastine (0.2, 0.25, 0.3, 0.4, 0.6 mg/kg i.p.; administered at the time of HCG).	Aneuploidy in metaphase II oocytes: hyperhaploidy	Significant increases of hyperhaploid oocytes at doses between 0.2 and 0.4 mg/kg. The percentages of hyperhaploid oocytes were 0.5 (1/218), 23.2 (149/641), 23.9 (81/339), 29.3 (72/246) and 30.7 (65/212), for controls, 0.2, 0.25, 0.3 and 0.4 mg/kg, respectively. At 0.6 mg/kg, almost all oocytes are arrested at the metaphase I stage.	[Mailhes et al. 1993]

KE4: Altered chromosome number	Mouse (Oocytes)	Vinblastine (0.6 mg/kg i.p.; administered at the time of HCG; oocytes harvested between 17 and 25 h after treatment).	Aneuploidy in metaphase II oocytes: hyperhaploidy	At all harvesting times, similar frequencies of hyperhaploid oocytes are observed, always higher than the control value. The percentages of hyperhaploid oocytes were 0.5 (1/190), 27.5 (47/171), 25.9 (42/162), 23.6 (47/199), 29.0 (47/162) and 23.4 (26/11), for controls and harvest +17, +19, +21. +23, +25 after 0.6 mg/kg, respectively. Conversely, a decrease of MI blocked oocytes is observed with time, paralleled by an increase of diploid metaphase II oocytes. These overall results mean that some oocytes may overcome the meiotic arrest induced by vinblastine without forming a functional spindle.	[Mailhes and Marchetti 1994]
KE4: Altered chromosome number	Mouse (Oocytes)	Vinblastine (0.06, 0.09 mg/kg i.p.; administered at the time of HCG to heterozygous Rb(3.8)Rma mice).	Aneuploidy in metaphase II oocytes: hyperhaploidy	Significant increases of hyperhaploid oocytes at both doses. Since the Lowest Effective Tested Dose in mice with standard karyotype is 0.2 mg/kg, this data suggest that sensitivity to chromosome segregation errors may change with karyotype.	[Pacchierotti et al. 1995]
KE4: Altered chromosome number	Chinese hamster (Oocytes)	Vinblastine (3 mg/kg i.p.; at the onset of the first meiotic spindle formation, i.e.16 h before oocyte harvest).	Aneuploidy in metaphase II oocytes: hyperhaploidy	Statistically significant increase of hyperhaploid oocytes over the control value. The percentages of hyperhaploid oocytes were 1.5 (3/198) and 82.1 (128/156) for controls and 3 mg/kg, respectively. The magnitude of the effect is similar to that elicited in the mouse by a 10 times lower dose.	[Tateno et al. 1995]
KE4: Altered chromosome number	Mouse (Oocytes)	-	Disregulation of chromosome segregation as a function of Bub1 activity	In the absence of Bub1 function, spectral karyotyping shows that 5 to 30 % of bivalents undergo non-disjunction.	[McGuinness et al. 2009]

KE4: Altered chromosome number	Mouse (Oocytes)	-	Disregulation of chromosome missegregation as a function of an MTOC-associated protein concentration.	Depletion of a MTOC component induces a significant increase of aneuploid oocytes from about 5 to over 40%	[Ou et al. 2010]
KE4: Altered chromosome number	Mouse (Oocytes)	-	Presence and fate of non-aligned bivalents at anaphase onset	Live imaging of 51 oocytes at the first meiotic division shows that, at anapahse onset, 2 of them (4 %) have not yet congressed at the metaphase plate and eventually undergo non-disjunction.	[Lane et al. 2012]
KE4: Altered chromosome number	Mouse (zygotes)	Colchicine (Dose response: 2.0, 3.0, 4.0 mg/kg by gavage; administered at the time of HCG).	Hyperploidy	Significant increase of hyperploid zygotes over the control value at all doses tested. The percentages of hyperhaploid zygotes were 0.6 (2/237), 5.4 (21/389), 14.3 (62/435), 15.8 (69/438), and 25.1 (98/391) for controls, 1.0, 2.0, 3.0, and 4.0 mg/kg, respectively Comparison of these data with those obtained in oocytes under the same experimental conditions support the notion that aneuploid oocytes can be fertilized and the chromosome defect is transmitted to the embryo.	[Mailhes et al. 1990]

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